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A Retrospective Analysis of the Safety and Efficacy of a 6-Week Pulmonary Rehabilitation Program in Patients with Severe Pulmonary Arterial Hypertension

by

Gerald Brian Miciak

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Abstract

Pulmonary Arterial Hypertension (PAH) is progressive disease characterized by reduced exercise capacity and decreased quality of life. Despite the availability of disease targeted therapies outcomes remain sub-optimal. Pulmonary Rehabilitation has proven to improve outcomes in other chronic respiratory disease, but evidence is limited in PAH. We provide preliminary information on the safety and efficacy of a six-week pulmonary rehabilitation program (PRP) in patients with severe PAH. We analyzed the outcomes for 42 patients that completed the 6-week program. Overall there was a +7.4m (95% CI [-6.7, 21.6]) increase in the 6MWD and quality of life scores improved. All 42 patients completed the program and no adverse events were reported. Our study demonstrated the safety of PR in this group of patients and identified a group of patients with preserved cardiac function (i.e. cardiac output) who appear to have a clinically significant improvement in their exercise capacity and HRQL.

Table of Contents

List of Tables

List of Figures

CHAPTER I: Introduction

Pulmonary arterial hypertension (PAH) is a rare, complex, and life threatening chronic lung disease. PAH causes severe limitations in daily functional abilities, reduces quality of life, and has a high mortality rate - with the first prospective national registry in 1991 reporting a median survival of 2.8 years(1). Over the last 30 years, a wealth of research has improved the understanding of the pathobiology and pathophysiology of PAH leading to the development of treatment options for this devastating disease(2). Current treatment options are associated with modest improvements in functional, symptomatic, and hemodynamic outcomes. The results of a recent meta-analysis demonstrate that existing treatments have improved survival but mortality rates continue to be unacceptably high and functional, quality of life, and hemodynamic impairments remain severe in many patients(3). Additional adjunctive measures are warranted to try and improve upon the outcomes achieved with existing treatment options.

Research evaluating adjunctive treatment measures to improve outcomes in PAH is emerging. Pulmonary rehabilitation (PR) in this paper refers to the exercise training component of the pulmonary rehabilitation program. PR is one form of adjunctive treatment that has emerged in recent years for PAH but has not been thoroughly investigated. PR has been researched extensively in Chronic Obstructive Pulmonary Disease (COPD) and has been

proven to be an effective adjunctive treatment to improve outcomes in COPD(4). Research for pulmonary rehabilitation in PAH is limited and primarily has focused on patients with stable PAH and mild physical limitations. The delay in investigating pulmonary rehabilitation in PAH is explained by the historical concept within the PAH expert community that considered exercise detrimental to PAH patients because of hemodynamic instability(5). In the last 7 years research has demonstrated Pulmonary Rehabilitation to be safe and effective in small, short-term studies focusing on mildly impaired stable PAH patients(6-10). Additional research to evaluate pulmonary rehabilitation's safety and efficacy in severely compromised patients would add to current information available and help define its role in future management guidelines for PAH. The objective for this research project was to investigate the efficacy and safety of PR in severely compromised PAH patients.

1.1 Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a serious chronic disorder of the pre-capillary pulmonary circulation. It is a progressive condition caused by structural and functional changes in the pulmonary vasculature, resulting in increased pressure in the pulmonary arteries, which may ultimately lead to failure of the cardiorespiratory system often resulting in severe functional impairment and causing death(2). PAH is hemodynamically defined as; sustained elevation of mean pulmonary arterial pressure (mPAP) $\geq$ 25mmHg

and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, with a normal or reduced cardiac output when measured with right heart catheterization(11). PAH is considered to be a rare condition that is idiopathic in cause or associated with a variety of causes including; heritable, drugs- and toxins-induced, and may be associated with other medical conditions(12).

1.1.1 Diagnosis

The diagnosis of PAH is complicated and usually made by a physician with expertise in PAH. It is probable for early PAH to go unrecognized by physicians not familiar with the disease, causing a delay in the diagnosis until a patient has progressed to an advanced stage of the disease with severe physical and clinically overt signs and symptoms.

Once there is a suspicion of PAH there is a series of investigations performed to confirm or exclude the diagnosis. Patients will be assessed by their clinical presentation and a series of the following non-invasive studies that detect signs and/or symptoms associated with PAH can be performed. An electrocardiogram is used to detect RV changes often associated with PAH (RV hypertrophy and strain, right atrial hypertrophy)(13). The chest radiograph can identify central pulmonary arterial dilatation and/or 'pruning' of the peripheral blood vessels, and/or right heart enlargement(13). Pulmonary function tests and arterial blood gases help to

identify underlying airway or parenchymal lung diseases(13). Echocardiography is used to evaluate several cardiac variables (estimated pulmonary arterial pressure (PAP), tricuspid regurgitation velocities, measurements of right heart chamber sizes and wall thickness, and interventricular septum shape and function) that identify cardiac abnormalities associated with PAH(13). Finally, ventilation/perfusion lung scans are done to look for a potential surgically treatable form of PH; chronic thromboembolic pulmonary hypertension (CTEPH)(13).

If there is a high suspicion of PAH from the clinical presentation and the series of non-invasive investigations, the diagnosis is usually confirmed by right heart catheterization (RHC). The RHC is a procedure where a catheter is guided through the central venous system into the chambers of the heart and the large pulmonary arteries. The RHC is considered the 'gold standard' for disease confirmation because of its accuracy in measuring hemodynamics(14). It provides hemodynamic measurements for systemic blood pressure and saturation, pulmonary arterial pressure and saturation, pulmonary capillary wedge pressure, right atrial pressure, cardiac output, and pulmonary vascular resistance (12). Additional measurements beyond the measurements used in the diagnosis of PAH can be collected during the RHC and used to monitor the clinical course of the patient. Table 1 provides definitions and values of right heart catheter measurements used in PAH.

Table 1 Right Heart Catheter Measurements used in PAH

Measurement	Definition	Normal values at rest (Range)
Mean Pulmonary Artery Pressure (mPAP)	The average pressure in the pulmonary artery over the course of one heart beat.	**14 (8-20) mmHg**
Cardiac Output (CO)	The volume of blood being pumped by the heart, in particular by a left or right ventricle in the time interval of one minute.	**4-8 L/min**
Cardiac Index (CI)	A vasodynamic parameter that relates the cardiac output (CO) to body surface area (BSA), thus relating heart performance to the size of the individual.	**2.6-4.2 L/min/m^2**
Pulmonary Capillary Wedge Pressure (PCWP)	Also referred to as the pulmonary artery occlusion pressure. It is the indirect measure of the pressure on the left side of the heart. Its measurement is obtained by wedging or occluding the pulmonary artery with a small balloon on a catheter tightly enough to block blood flow from behind, therefore give a sample of the pressure beyond the balloon.	**9 (4-12)**
Right Atrial Pressure (RAP)	Atrial pressure is the pressure, which the blood exerts on the atrial walls. It also describes the pressure of blood in the thoracic vena cava, near the right atrium of the heart. RAP reflects the amount of blood returning to the heart and the ability of the heart to pump the blood into the arterial system.	**6 (2-7) mmHg**
Pulmonary Vascular Resistance (PVR)	PVR is a measurement of the amount of resistance to flow that must be overcome to force blood through the vascular of the lung.	**70 (20-130) dyn*sec/cm^5**

Revised from: Davidson CJ, Bonow RO. Cardiac catheterization. In: Libby P, Bonow RO, Mann DL, Zipes DE. *Braunwald's Heart Disease*. 2 vols. 8th ed. Philadelphia, PA: Saunders Elsevier; 2008:439-463.

1.1.2 Pathophysiology

The pulmonary circulation is a low-pressure, high-flow system with a capacity to recruit unperfused vessels to meet increased metabolic requirements during physical activity(15). To meet the increased gas exchange requirements (oxygen delivery and carbon dioxide removal) during physical activity, ventilation and cardiac output (CO) are increased(16). The healthy lung maintains a low-pressure and high flow state during increased metabolic demand by increasing circulation through recruitment and distention of the pulmonary capillaries (16). These compensatory mechanisms maintain a low pulmonary vascular resistance, minimizing the increase in workload of the right heart during physical activity (16).

In PAH there are complex and multifactorial pathophysiological changes in the pulmonary vasculature that compromise the normal cardiorespiratory physiological response to increased metabolic requirements(17). Vascular injury and endothelial dysfunction occur along with a disruption in the balance of vascular effectors within the arterial wall(17,18). Vascular mediator changes identified in the pathogenesis of PAH include decreased production of vasodilatory/anti-smooth muscle cell proliferative factors (prostacyclin, nitric oxide, and vasoactive intestinal peptide [VIP]), and increased production of vasoconstrictive/pro-smooth muscle cell proliferative factors (endothelin, thromboxane, serotonin)(17,18). This

imbalance of mediators leads to vasoconstriction and characteristic histopathologic changes in multiple cell types in the peripheral pulmonary arterial wall, including vascular proliferation, fibrosis, remodeling and vessel obstruction(17,18). These changes promote narrowing of the vessel lumen in the affected arteries making it difficult for the blood to pass through the lungs. This leads to increasing pulmonary vascular resistance (PVR), subsequently leading to an increasing workload for the right ventricle to pump blood through the compromised pulmonary circulation. This extra effort leads to right ventricular hypertrophy, ultimately leading to right ventricular failure and death (11).

1.1.3 Clinical Presentation

The clinical presentation of PAH can be described by the continuum of hemodynamic changes that occur with disease progression. The progression of the pathophysiological changes, resulting in inadequate oxygen delivery to meet the demands of cellular respiration impedes cardiopulmonary and skeletal muscle responses during physical activity. This results in decreased aerobic metabolism and early muscle fatigue during aerobic activity(19). Early in the course of the disease patients are asymptomatic, their CO is normal at rest and during exercise because the right ventricle is able to adapt to its increased workload caused by the increase in PVR. Eventually the right heart cannot sufficiently increase CO caused by the increasing PVR. This will lead to exertional dyspnea and fatigue due to inadequate oxygen delivery by the insufficient right heart increase in CO. Further progression of the disease

leads to further decline in CO and decreasing activity tolerance, along with signs of right heart failure (peripheral edema, ascites and jugular venous distension). Other less common symptoms that can occur during the progression of the disease include: cardiac arrhythmias, dizziness and syncope due to decreased cerebral blood flow; and chest pain, caused by inadequate cardiac blood supply.

1.1.4 Classification

The current classification categorizes pulmonary hypertension (PH) into 5 categories based on pathologic and clinical features, and therapeutic treatments (12). (See Table 2) For the purpose of this research the main category of interest is Group 1 PAH. This group (Group 1) is comprised of sub-categories of the following: idiopathic and heritable PAH, drug and toxin-induced PAH, PAH associated with connective tissue diseases, HIV infection, porto-pulmonary hypertension, congenital heart diseases, schistosomiasis, and chronic hemolytic anemia(12). All of these sub-categories within Group 1 share similar pathophysiologic characteristics, clinical presentation and have similar treatment approaches (12). The other major categories, group 2-5, are caused by underlying medical conditions (i.e. left heart disease, lung diseases, and chronic thromboembolism), and the management of these forms of pulmonary hypertension differs from Group 1. Classifying the type of pulmonary hypertension at diagnosis is important as it allows for the appropriate treatment strategy to be implemented for the individual patient.

Table 2. Clinical Classification of Pulmonary Hypertension

Clinical Classification of Pulmonary Hypertension
1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Adapted from: Proceedings of the 4th World Symposium on Pulmonary Hypertension, February 2008, Dana Point, California, USA. J Am Coll Cardiol 2009 Jun 30;54(1 Suppl):S1-117

1.1.5 Disease Severity and Outcome Measurements

In PAH disease severity can be assessed by several clinical outcome measurements that are divided into the following 3 categories: functional, quality of life, and hemodynamic. These measurements have been used on a clinical basis to follow health status and in research to evaluate the outcomes with medical interventions.

1.1.5.1 Functional Assessment

Functional assessment in PAH refers to evaluation of the individual's capacity to carry out physical activities. Objective and subjective assessments are used to evaluate functional assessment and this is performed either with tests in controlled-standardized settings or daily by measuring daily activities. In controlled-standardized tests, patients' functional assessment is usually measured by exercise capacity. The most common exercise capacity evaluations used in PAH have been the six-minute walk test (6MWT) and cardiopulmonary exercise tests (CPET). Exercise capacity tests are frequently used in evaluation of PAH patients because of their ability to quantify the pathophysiological severity of PAH(20), their prognostic capability (21,22), and the correlation between their measured improvements and the patient's symptoms (23). A functional assessment used to classify PAH patients based on the ability to perform everyday daily activities is the World Health Organization Classification of Functional Capacity (WHO FC), an adaptation of the New York Heat Association (NYHA)

functional class(24)(see Table 3). This subjective measurement quantifies a patients' exertional intolerance, and provides a way to evaluate the patient's ability to perform daily activities. WHO FC has been shown to be useful in evaluating PAH patients' risk of death(1) and the survival rate upon initiation of therapy(25).

Table 3: World Health Organization Classification of Functional Status of Patients With Pulmonary Hypertension

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Adapted from Barst et al. Diagnosis and differential assessment of pulmonary arterial hypertension, 2004 (24)

1.1.5.2 Quality of Life Assessment

Quality of Life (QoL) is generally becoming a more important clinical outcome measurement in health-care practice and research (26), including PAH. QoL instruments are utilized to capture information regarding an individual's self-evaluation of life areas that one considers important (27). Health-related quality of life (HRQL) specifically refers to the subjectively perceived impact of one's health on the physical, psychological, and social domains (26-28). To date HRQL instruments that have been used in research and clinical practice settings to evaluate outcomes in PAH patients include: the St. George's Respiratory Questionnaire, the Minnesota Living with Heart Failure (MLHF) Questionnaire, the Chronic Heart Failure Questionnaire, Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) Questionnaire, and the Medical Outcomes Study Short Form-36 (SF-36) Questionnaire (29-31). Important information for PAH has been collected from studies that have utilized HRQL instruments. HRQL scores correlate with other PAH clinical outcome measurements, and importantly these instruments are able to assess the level of impairment perceived by the PAH patient(30). HRQL tools are noninvasive-easy to use instruments that provide important information to understand the impact of disease and the changes interventions provide regarding the level of disability and well being of patients with PAH.

1.1.5.3 Hemodynamic Assessment

Currently right heart catheterization (RHC) and echocardiography measurements are the main hemodynamic evaluations utilized as clinical outcome measurements for PAH. Both generate many indices but only certain indices have proven to have important prognostic value in the PAH patient.

RHC provides direct and accurate hemodynamic measurements. RHC measurements are an important predictor of survival, and RHC values collected in the NIH registry have been used to formulate an equation used to estimate survival in PAH(1). RHC is therefore a useful assessment that can provide information on the severity of the disease and responses to therapy, but the risks of the invasive RHC procedure limit the frequency in which it is performed in the ongoing assessment of disease severity.

Echocardiography is frequently used to diagnose and evaluate outcomes in PAH patients. It is a noninvasive technique with little risk and can be repeated serially. Although less sensitive than RHC, echocardiography still provides information on cardiac function and is a valuable instrument in assessing the severity and prognosis of PAH (14). It also has been shown to be sensitive enough to demonstrate clinical changes with treatment. Indices that are most relevant for assessment in PAH patients include; right atrial

(RA) and right ventricular (RV) enlargement, reduced RV function, displacement of the intraventricular septum, and tricuspid regurgitation. (14) Other variables that can be measured include estimated pulmonary arterial systolic pressures, and the presence of pericardial effusion (14).

1.1.6 Treatment

Surgical treatment options (i.e. heart and/or lung transplantation, and atrial septostomy) were the first and only treatment options available for PAH patients prior to the development of PAH targeted pharmacologic treatments. Patients with PAH can have heart-lung, single or double lung transplantation, and the choice of transplantation is centre dependent and based on donor organ availability. In the current era of PAH pharmacologic treatments, heart and/or lung transplantation is now reserved for those patients that fail PAH targeted treatments(13). Survival of PAH patients that undergo single, double-lung or heart and lung transplantation is 45-50% at 5 years, with continued good quality of life, which is comparable to the survival of other diagnosis indicated for heart and/or lung transplantation(32). Even with comparable survival rates to other diagnosis indicated for lung transplantation, the number of PAH patients undergoing lung transplantation only accounted for 3.1% of the reported lung transplants performed internationally from 1995-2011(32). The other surgical treatment option for PAH patients is a procedure known as atrial septostomy, which is the creation of an inter-atrial shunt to decrease the elevated pressure in the right

heart chambers which results from the increased pulmonary resistance secondary to the pathophysiological changes taking place in the pulmonary vasculature. There is evidence to demonstrate an improvement in functional capacity and improved hemodynamics with this surgical option, but long-term survival has not been studied(13). At this time atrial septostomy is reserved as a palliative or bridging option procedure in a very limited number of treatment centres(13).

The introduction of drug treatment options has allowed more patients access to treatments that improve the daily function, quality of life, and delay the progression of the disease. (33-35) The availability of these medications has increased the awareness and recognition of PAH , leading to earlier intervention and better patient management. Despite these advances the disease still has a significant impact on patients' functional capacity and quality of life, and the mortality rate still remains high (2). Research is ongoing with the goal of identifying new pharmacotherapies to hopefully further improve individuals' daily function and long-term outcomes (2).

The first pharmacologic treatment for PAH, intravenous epoprostenol, became available in 1995. Since then, 5 additional drugs have been approved in Canada. In other countries an additional 4 drugs are currently available, for a total of 10 PAH targeted drugs. These drugs belong to 3 pharmacological classes that target 3 main pathways; endothelin, nitric

oxide, and prostacyclin, shown to be involved with the abnormal proliferation and contraction of the smooth-muscle cells of the pulmonary arteries in patients with PAH(36). The controlled clinical trials with PAH targeted drugs have proven that these agents improve the functional capacity of patients and slow the progression of the disease (2,11). High dose calcium channel blockers, an additional class of drugs have demonstrated a clinical benefit in nonrandomized, uncontrolled studies in a very small population of PAH patients who are classified as vasodilator responders(2,11).

Treatment strategies for PAH with the current treatment options have been published as an evidence-based treatment algorithm(12) and/or expert consensus documents(11,37). The experience and evidence have increased with PAH targeted therapies and treatment approaches with pharmacologic agents now include initiating drug therapy earlier in the course of the disease (i.e. WHO FC II) and using combinations of drug therapies from each of the 3 classes. Combination treatment has also evolved from adding on a second drug when a patient symptomatically worsens, to adding on additional drug from each class until a patient achieves predetermined treatment outcomes (11,12,37). These treatment goals are based on the prognostic predictors of survival in PAH (11,12,37).

Currently, adjunctive treatment measures like pulmonary rehabilitation (exercise training) are not given strong recommendations in the current

management guidelines due to conflicting evidence available to demonstrate the efficacy and safety in the PAH population (11). However, there is a growing body of evidence to support this treatment option in other forms of chronic lung disease. Further improvement in functional capacity, quality of life, and long term outcomes is still required for PAH patients. The limited treatment options for patients that continue to deteriorate on PAH targeted treatments and reach a severely compromised stage warrants further investigation to evaluate additional treatment modalities, such as pulmonary rehabilitation, to determine if they provide additional improvement in patient outcomes. A more comprehensive discussion of pulmonary rehabilitation in PAH will be covered in the next section.

1.2 Pulmonary Rehabilitation (PR)

1.2.1 Introduction

Pulmonary rehabilitation (PR) is a well-established adjunctive form of therapy with exercise training as an essential component. PR is used to enhance standard forms of therapy in certain chronic lung diseases to improve clinical outcomes. The evidence-based support for PR in chronic respiratory diseases primarily comes from research in the Chronic Obstructive Pulmonary Disease (COPD) population. Research has demonstrated that PR provides significant clinical improvements in the COPD population. Guidelines(38,39) for the applications of PR in COPD have been developed and also include recommendations for program composition and

outcomes.

The primary goals of PR in COPD focus on the improvement in the physical and psychosocial functioning of the patients. (38-40) To assess the safety and benefits of PR in COPD patients, the outcomes measured have focused on adverse events and the assessment of the changes in disease associated symptoms (exercise capacity and HRQL outcomes).

Dyspnea is a primary symptom in COPD and tools to assess the improvement in dyspnea are frequently used in studies that evaluate the impact of PR in COPD. Studies evaluating PR in COPD have used the Borg dyspnea scale (41-43) and the Visual Analog Scale (VAS) (44-46) to determine how short of breath or fatigued an individual is at the time of participation in the exercise training session and at the end of the program. The BORG scale (42,43) and dyspnea VAS (44,46) have been shown to improve after PR. Recently Ries et al. (47) defined the Minimally Clinical Important Difference (MCID) as a change in 2.0 units for the BORG Dyspnea score and 10 to 20 units for the VAS in response to PR in COPD patients.

Improving exercise capacity is a primary goal of PR programs and the improvements it provides in COPD patients has been thoroughly investigated. (48,49) Outcomes from PR have been measured with functional exercise capacity or maximal exercise capacity tests. The six-minute walk

test (6MWT) is one functional exercise capacity test predominantly used to evaluate outcomes from PR. The 6MWT is a simple, well-validated and standardized test for evaluating exercise capacity outcomes in chronic lung diseases. (23) Recent meta-analyses of PR in COPD have concluded that PR has a significant impact on functional exercise capacity(48,50). These meta-analyses showed an improvement in six-minute walk distance of +48m (95% CI: 32 to 65m) (48) and +50.6m (95% CI: 30.3 to70.8m) (50). The results were consistent amongst the studies even when there was program heterogeneity in relation to the program duration, number of sessions, training intensity, and patient demographics.

HRQL improvement is another primary outcome for PR in COPD. HRQL outcomes have been assessed with generic or respiratory-specific HRQL tools such as: the SF-36, Chronic Respiratory Disease Questionnaire (CRQ), or the Saint George's Respiratory Questionnaire (SGRQ). HRQL outcomes reported in several meta-analyses concluded there is an improvement in HRQL parameters used to assess the impact of PR in COPD(48-50). When analyzed the majority of studies exceeded the MCID(49,50). In COPD HRQL improvements have been observed after PR even in the absence of clinically significant improvements in exercise capacity.(49)

To date Level 1A evidence is available for PR demonstrating it improves dyspnea and the HRQL of patients with COPD(39). Robust research results

have allowed integration of PR into the management guidelines of COPD patients, but the lack of evidence for PR in other chronic respiratory diseases (i.e. PAH) does not allow for a strong level of recommendation in PAH management guidelines. However, the evidence and experience with PR in COPD have been used as a template to start the preliminary evaluation of safety and benefits in other chronic respiratory diseases. Before PR can be recognized as a standard of care and integrated in other chronic lung disease management guidelines the safety and benefits will need to be well defined.

1.2.2 Pulmonary Rehabilitation Program – Definition and Composition

Pulmonary rehabilitation has been most recently defined by the American Thoracic Society and European Respiratory Society as: *"an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities."* (38) In chronic lung diseases, like COPD, PR is integrated into the individualized treatment of the patient to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease(38).

Currently Pulmonary Rehabilitation programs include various combinations of several components; including exercise training, education, psychosocial support, and occupational therapy. Of these, exercise training is the only

component with Level 1A evidence and consequently designated as mandatory in PR COPD guidelines(39). The other components of PR programs have weaker and inconclusive evidence to support their contribution to the improved outcomes in COPD patients, but are included in programs because of expert recommendation(38,39). These components are supplemental to exercise training and are incorporated into a program based on the specific needs of the individual patient. For a PR program to be designated as a comprehensive program it must include a mandatory exercise training program and provide a minimum of one other component(39).

Additional to the basic components that make up the PR program, other features in the composition of a PR program include tailoring the program based on the needs of the specific chronic lung disease and individual patient, and a multidisciplinary team of health care professionals to facilitate the program(39). Assessment of each individual patient by the multidisciplinary team should occur before entry into the program to ensure that a safe and effective individualized program is designed for the patient to achieve the goals of improving the physical and social function of the patient.

1.2.2.1 Rehabilitative Exercise Training – *'Essential Component'*

Rehabilitative exercise training is the essential component of PR(39). It is designed to stimulate the deconditioned cardiovascular and skeletal muscle systems, and improve other systemic manifestations of chronic respiratory diseases(49). Exercise training has the most significant impact on the physiologic factors that produce the limitations in exercise tolerance, compared to all the other components of PR (38). The pathophysiologic factors that are targeted by PR include: ventilator limitation, gas exchange limitation, cardiac dysfunction, skeletal muscle dysfunction, and respiratory muscle dysfunction(38). Impairment of lung function is the primary deficit of all chronic lung diseases (i.e. COPD, PAH), but extrapulmonary manifestations, like skeletal-muscle dysfunction also contribute significantly to the exercise intolerance(4). The skeletal-muscle dysfunction that occurs in chronic lung diseases is a result of reduced aerobic capacity, leading to an early onset of lactic acidosis, which will present as muscle fatigue and be the primary factor limiting exercise tolerance (4). Changes in skeletal-muscle function after exercise training has been observed(38), and it is believed that improved skeletal muscle-function is a major contributor to the benefits of PR, as PR does not alter lung mechanics and gas exchange(4).

Endurance exercise training of the lower limbs is usually the core focus of rehabilitative exercise training (39), and upper limb training and/or strength training can be included in some circumstances as part of the program. The intensity of the training is dependent on the patient and/or chronic

respiratory condition and can be adjusted (increased or decreased) during the program based on the patient evaluation of the observing health care professional(4,38,39). The intensity of the exercise training has been evaluated for PR, and it appears that either high intensity or low intensity training have proven positive outcomes for patients with chronic respiratory lung diseases(51). Guidelines however suggest higher intensity training may provide better outcomes, but still suggest individualization of the intensity of the training to an individual's disease severity, symptom limitations, co-morbidities, and level of motivation(38). A level of exercise training intensity of 60% of peak exercise capacity has been suggested to achieve a safe and effective outcome on changes in exercise capacity(4,38,39). The number of sessions usually ranges between 3 and 5 sessions a week with the duration of the program between 6 and 12 weeks(38,49,52). The training sessions are organized as an in-patient or outpatient program, and home-based training programs are feasible, usually after a short in-patient or outpatient session. Proper patient assessment, which should include an evaluation of the current disease management, disease severity, HRQL, and exercise tolerance, of the individual patient needs to be conducted to assure PR will be safe for the individual. Baseline and follow up evaluation is necessary to measure the outcomes to assess the efficacy of PR (49).

1.2.3 Pulmonary Rehabilitation in PAH

The definition of PR recommends intervention for symptomatic patients with

chronic respiratory disease who have decreased ability to perform daily life activities (38), but only recently has there been an expanded research interest to study PR as an adjunctive treatment for pulmonary arterial hypertension (PAH). Prior to 2005 there were no published studies describing the safety and efficacy of PR in the PAH patient population. Expert recommendation was to avoid PR (exercise training) in this population because of the perceived notion that exercise training could be detrimental in PAH patients (5). However, research in the past 8 years has provided some information regarding the safety and efficacy of PR in PAH patients. The current level of evidence still has not lead to a consensus amongst PAH experts on how and for whom to recommend PR as an adjunctive treatment for PAH patients (53), and currently PR is still not included or has a weak recommendation as an adjunctive treatment to pharmacotherapy in the most recent PAH evidence-based treatment guidelines (11,37).

The first study to report the findings for PR as an adjunctive treatment in a cohort of PAH patients was in 2005 (6), and since then there have been 7 additional studies evaluating the safety and beneficial effects related to exercise endurance, HRQL and skeletal muscle dysfunction in various patient PAH populations published (7-10,54-56).

The first study in PAH evaluating PR by Uchi et al (6) reported the effects of a 6 to 8 week PR program on 24 subjects with iPAH. The patients that

participated in this study were NHYA FC III or IV (15 and 9 patients, respectively) who received continuous intravenous prostacyclin administration. The PR program was 5days/week with each session being 30-60 minutes in duration. This study demonstrated significant improvement in 6MWD (P = 0.001), improved NYHA FC (p = 0.010), increased lower extremity strength (p < 0.001), and decreased heart rate (p = 0.007) at rest. No adverse events were reported during the course of the study. The second published study by Mereles et al. (7) reported the effects of a 15-week comprehensive program in 30 PH (PAH, n=24, inoperable chronic thromboembolic pulmonary hypertension (CTEP), n=6) subjects. The patients that participated in this study were WHO FC II-IV (20% FC II and 73% FCIII) on optimal and stable treatment; either monotherapy (43%) or a combination of 2 or 3 PAH targeted treatments that remained unchanged during the course of the PR program. The PR program was 5-days/week for 30-60 minutes duration, with the initial 3 weeks consisting of an in-hospital program, followed by 12-week program based out of the patients home. Patients were randomized 1:1 to either the control group or the training group and patients were assessed at baseline, week 3 and 15. After 15 weeks the PR group demonstrated an improved 6MWT distance (96 ± 61m), improved HRQL scores (7 scales of the SF-36 improved significantly), and improved FC (2.8±0.6 to 2.3±0.4). Borg dyspnea scale scores, hemodynamic echocardiographic measurements and gas exchange measurements remained unchanged. All patients tolerated the PR program and had no reported

adverse events. These 2 studies demonstrate that PR is safe in moderately impaired and stable PAH patients with a positive outcome for exercise capacity (i.e. 6MWT), functional status and HRQL outcomes.

Muscle dysfunction has been reported in PAH patients and is believed to be a cause of the symptoms and limitations of physical activity (57-60). Two groups have recently published their results on the effect of PR on exercise capacity and pathophysiological changes that occur to muscle function and structure in PAH patients. de Man et al. (9) reported the effects of PR on skeletal muscle function and morphology by evaluating quadriceps muscle dysfunction. The study evaluated a 12-week program in 19 clinically stable iPAH patients who had mild disease (WHO FC II, n=3, WHO FC III, n=16). Results demonstrated that PR changes muscle function (improved strength an endurance) and components of morphology, which are representative of muscle endurance improvement (increased number of capillaries per myocyte and improved oxidative enzyme activity in the form of increased succinate dehydrogenase activity in Type I and Type II muscle fibers). This study however did not demonstrate an improvement in 6MWT distance at the end of 12 weeks. CPET measurements showed no improvement in maximal exercise capacity but did show improvement in endurance, which is associated with the improvements seen in quadriceps muscle endurance. PR appeared to be safe in these patients studied as no adverse events were reported during the 12 week PR program. Mainguy et al. (8) also evaluated

muscle structure and function in PAH after PR and reported the changes to muscle characteristics and exercise capacity after a 12-week program in 5 iPAH subjects. Patients in this study also had a mild disease (WHOC FC II, n =3, WHO FC III, n=2). Using different analyses to analyze muscle characteristics than the previous study Mainguy et al. demonstrated the proportion of type IIx fibers significantly decreased, and the type I fiber surface and the capillaries/ fiber ratio tended to increase. These changes represent a less fatigable muscle profile and may have resulted in a higher anaerobic threshold, which may attribute to exercise endurance improvements. In this study mean 6MWT distance improved by +85m (p=0.01). Two adverse events were reported (progressive fatigue and recurrent dizziness) during the study. Results from these 2 studies on the effect of PR on muscle structure and function in PAH patients appears to be positive with the observed outcomes demonstrating improved muscle structure and function which could improve exercise tolerance and endurance.

More recent studies have either evaluated PR in PAH in larger cohorts of patients(10), other types of PR programs (54), or assessed the impact on longer-term outcomes(55) in PH patients. Grunig et al.(10)reported the results of a prospective study assessing the safety and efficacy of PR in various groups of PH. This prospective study looked at 183 patients including; iPAH, associated forms of PAH (drug or toxin induced, connective

tissue disease, HIV, portal hypertension, congenital heart defect), CTEPH, PH due to lung disease (obstructive lung disease, restrictive lung disease, or sleep apnea syndrome) or PH due to left heart disease. Within these groups 18 (9.8%) WHO-FC IV patients participated. At the end of the 15-week program 6MWT distance was improved by 78±49.5m ($p<0.001$) for the overall study sample, with all groups demonstrating a similar increase, except the 'associated PAH' group, which had a lower 6MWT improvement, compared to the iPAH group (56±49m vs. 85±49m, respectively). In the small sample of WHO FC-IV patients there was also an improvement in the 6MWT distance (63±61m, $p=0.01$), which trended to a greater percentage increase than the WHO FC II/III group. Other outcome measurements assessed also improved from baseline, including: CPET measurements, HRQL measurements, WHO FC, and hemodynamic measurements assessed with echocardiography. This study identified a group 26 patients that were defined as 'non-responders' to PR (defined as a < 5% increase in 6MWT distance from BL to week 15). Even though this group did not have an improved 6MWT , improvement in HRQL was significant and the scores were comparable to the group of patients that had a significant improvement in their 6MWT distance. The study was not able to identify differences in any clinical parameters between the 'non-responding' and 'responding' patient groups. The overall rate of serious adverse events was low in this study, with only 8 patients (4.3%) reporting acute serious adverse events (2 syncope, 6 pre-syncope). Overall, this study demonstrated that PR is effective and safe

in a monitored setting for a diverse group of PH patients, potentially including patients with more severe disease – i.e. WHO FC-IV. To evaluate if ambulatory rehabilitation (out-patient) programs would be safe and effective in PAH patients, Fox et al.(54)conducted a prospective randomized study that enrolled 22 stable PAH patients to either a 12 week out-patient PR program or to a control group that received standard of care PAH treatment, without participation in PR. The patients in this study were non-randomly assigned based on willingness and ability to attend a PR program. Patients included were PAH or CTEPH patients that were WHO FC II or III. The results of this study demonstrated an increase in exercise capacity showing an improvement in 6MWT distance of +32m in the group of patients that participated in the 12-week out-patient PR program compared to a decrease in 6MWT distance of -26m in the control group. The PR group also had improvements in CPET measurements: peak VO2 and peak work rate. There was no change in hemodynamic measurements assessed by echocardiography. From this study outpatient PR programs also appear to be safe as there was no reported adverse events during exercise training sessions. Finally, a study by Grunig et al. (55) evaluated the long-term safety and short-term effects (15 weeks) of an exercise training program in 58 patients who were prospectively followed for 24 ± 12 months. This study demonstrated an improved exercise capacity (6MWT increased 84± 49m, $p<0.001$) and HRQL (SF-36, 7 of 8 subscale scores improved) at 15 weeks and concluded exercise training may have good long-term safety in the PAH

patients but well-designed studies are required to investigate long-term effect on other parameters related to clinical outcomes.

Current published research for PR in PAH is limited to patients with stable disease and mild exercise function limitations. Studies required all patients to have stable disease, the majority of patients enrolled were classified as WHO FC II or III, and in 6 of the 7 studies mean 6MWDs at baseline were greater than 400m. 6MWD in theses studies are higher than those studies evaluating PAH targeted therapies (33,34); only one published study evaluating PAH targeted therapies in WHO-FC II patients(61) had a mean 6MWD at baseline greater than 400m. For this sample of PAH patients the evidence currently supports PR as a safe form of therapy. In all of the studies published to date PR had no or minimal adverse effects reported during or after the completion of the PR program. PR also appears effective to improve exercise function, as 6 of the 7 studies demonstrated a significant improvement in 6MWD from baseline measurements; increases being comparable to those studies evaluating PAH targeted treatments. However, in the limited number of trials published, one study was not able to demonstrate an improvement in 6MWD at the end of the PR program (9), and one study found a group of 'non-responders' (10) regarding an improved 6MWD after completion of the PR program. A small number of PAH patients were enrolled in these studies so there is insufficient evidence to determine if there is a specific patient group of patients that may benefit from

participation in a PR program. PR in COPD has a significant impact on HRQL outcomes. To date there have been limited analyses on the impact of HRQL outcomes in PAH; only 3 of the 7 studies measured the change in HRQL after PR(7,10,55). The current evidence indicates that PR improves HRQL outcomes in PAH patients(7,10,55).

The limited amount of research published to date and the limitations of the current studies warrants a need for additional research in PAH to better understand if PR is safe and effective for all PAH patients or if it is only suitable as an adjunctive treatment for a specific-defined category of PAH patients. Areas of research still exist to demonstrate the safety and efficacy for patients with severe disease and more limited exercise function (i.e.FC IV patients and patients with 6MWD less than 400m), sub-categories within WHO Group 1 PAH, and research to determine if predictors can be developed to identify responders from non-responders, and finally well-designed trials are required to determine the potential long term benefits (i.e. survival) for PR in PAH.

Chapter II: Study Design and Methods

2.1 Study Objectives

1. To investigate the efficacy of a six-week pulmonary rehabilitation program on physical function in PAH patients with severe disease and limited exercise function. Six-minute walk test distance from baseline distance (prior to initiation of a pulmonary rehabilitation program) to distance walked at completion of the program was assessed. Other assessments included: HRQL measurements and BORG dyspnea score changes from baseline to completion of program.
2. To investigate the safety of a six-week pulmonary rehabilitation program in PAH patients with severe disease and limited exercise function.

2.2 Study Design

This is a retrospective analysis of consecutive patients enrolled in a six-week pulmonary rehabilitation program to assess the efficacy and safety of a six-week pulmonary rehabilitation program on clinical outcome measurements in PAH patients with severe disease and limited exercise function. All patients that were referred and participated in the preoperative six-week pulmonary rehabilitation program at the University of Alberta Hospital Lung Transplant Program will be analyzed. This study received prior approval from the Health Research Ethics Board.

2.3 Six-Week Pulmonary Rehabilitation Protocol

Patients participated in six weeks of daily (Monday-Friday) exercise/activity sessions in the Department of Physical Therapy. These sessions include an initial assessment phase, six-week pulmonary rehabilitation phase, and post-pulmonary rehabilitation phase.

The six-week pulmonary rehabilitation phase consisted of an assessment of exercise capacity by a single 6-minute walk test based on standardized conditions (23). Additional functional assessments included: overall range of movement, posture, balance, strength and aerobic capacity, supplemental oxygen needs for exercise and activity, and lifestyle/occupational expectations. The exercise sessions consist of a progressive individualized program including; aerobic training with treadmill and/or bicycle ergometry, extremity and core strength training with free weights and resistive equipment, balance training, stretching/flexibility activities and postural correction. The physical therapy sessions also include evaluation of relative contribution(s) of co-morbidities, treatment of co-existing musculoskeletal problems, and instruction on independent self-care and wellness.

2.4 Study Subjects

All adult patients with a confirmed RHC diagnosis of WHO Class I PAH that have completed the six-week Preoperative Pulmonary Rehabilitation Program (PPRP) between 1998 and 2010 were included in the cohort of patients for this study.

Inclusion Criteria:

All subjects to be included in the analysis must meet the following eligibility criteria to be included in the data analysis:

- Males and females aged 18 years or older.
- WHO Group 1 (Dana Point 2009 Definition – Table 2) PAH (PAH assessed by Right Heart Catheterization)
- Functional Class III-IV (1998 WHO Classification)
- Mean Pulmonary arterial pressure >25mmHg at rest; pulmonary capillary wedge pressure <15mmHg as per right heart catheterization.
- Listed for Lung Transplantation at the University of Alberta Lung Transplant program , and participated in the six-week preoperative pulmonary rehabilitation program.

Exclusion Criteria:

All patients that meet the above criteria for this case series were identified and included in this trial. For those patients that met the criteria but did not complete the six-week program or for those with missing data, patient baseline characteristics and reasons for not completing the program or for missing data will be reported in the results section of the baseline characteristics. Characteristics of these patients will be analyzed to see if there are differences amongst this sample of patients compared to the patients that completed the 6-week program.

2.5 Methods

In this cohort, patient specific data was extracted from the University of Alberta Hospital Lung Transplant database. The transplant nurse(s) managed this database. All data collected in the database was entered or reviewed by the nurse(s) responsible for the database. Data entered into the database was collected from the patients' medical charts and/or the six-minute walk report that was completed by the supervising physiotherapist. A search of the database was conducted to identify all eligible PAH patients that enrolled in the PPRP. The observed study endpoints collected included baseline measurements and measurements at the end of the six-week pulmonary rehabilitation program. The data extracted from the database included:

- Patient demographics (Age, sex, weight, PAH etiology, referral date to clinic, PAH treatments, etc.). Patient demographics were collected from the medical charts of each individual subject that participated in the 6-week PRP.
- Outcome measurements (6MWD, Borg dyspnea scale, Health Related Quality of Life questionnaires (Medical Outcomes Study Short Form-36 (SF-36), Chronic Respiratory Questionnaire (CRQ)). The supervising physiotherapist collected outcome measurements by the six-minute walk test report and the patient completed HRQL questionnaires and the transplant nurse(s) responsible for managing the database transferred results from these documents into the database.

- Safety Assessments – death, hospitalization, withdrawn from program because of disease worsening, symptoms during exercise (syncope, dizziness, chest pain, arrhythmias, acute right heart failure, emergency room visits, and hospital admissions). Safety assessments were reported by the supervising physiotherapist during the subjects' participation in the 6-week PRP program and entered into the medical charts. The transplant nurse(s) responsible for managing the database then transferred the collected safety information to the database.
- The data from the database was abstracted and transferred to STATA 12 and SPSS 19 software for analysis.

2.6 Statistical Analysis

Descriptive Statistics were used to illustrate the patient cohort analyzed (including means and standard deviations, medians and ranges or frequency counts and percentages).

Statistical significance for the efficacy main outcomes; change in six-minute walk distance and health related quality of life measurements (SF-36 and CRQ) in the cohort, before and after the 6 week pulmonary rehabilitation program were determined using paired t-tests and sign tests.

Adjusted average changes in main outcomes post intervention were studied using random effects models. Adjustment were made for sex, age, PAH diagnosis, 6MWD, mean pulmonary artery pressure (mPAP), right atrial pressure (RAP), cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR), PAH treatment, and baseline functional class (FC). The study patients were divided into two groups based on the change in 6MWD after the intervention: 1-increased (*responders)*; 2-decreased or remained same. (*non-responders*). Mean changes in HRQL indicators for the two sub groups were examined using paired t-tests. Baseline characteristics of the two sub groups were compared. To study the factors that influence the increment in 6MWD, a logistic regression analyses of the outcome were performed using a fitted univariable logistic regression of the increment 6MWD (yes=1; decreased or remained same=0) with each of the variables: gender, age, PAH diagnosis, mPAP, RAP, CO, CI, PVR, pulmonary capillary wedge pressure (PCWP), trans pulmonary gradient (TPG), PAH treatment and FC at baseline. Variables found with significance at p=0.20 in the univariable regressions were considered candidates for a multivariable model. In the multivariable model, variables that were significant at p=0.05 were retained in the model. All the other variables were removed from the model unless they were possible confounders. All the first order interactions between the variables were tested using Z-tests. The final model will consists of all significant variables, possible confounders and interactions if any. The analysis was done using statistical packages STATA 12 and SPSS 19.

Chapter III: Results

3.1 Study Subjects

We studied 43 patients with severe PAH and limited exercise capacity to assess the efficacy and safety of a Pulmonary Rehabilitation Program (PRP) in this patient sample. The patients included in the cohort were enrolled in the Pulmonary Rehabilitation Program between 1998 and 2010. All 43 patients meeting inclusion criteria completed the assessment phase of the program. One patient did not start the PRP because this individual experienced rapid deterioration in their condition, which required immediate bilateral lung transplantation surgery prior to the initiation of the PRP. This patient's baseline measurements and characteristics were included in the study baseline patient characteristics (see Table 4) but the outcome analysis was based on the 42 patients that completed the 6-week PRP, defined as having outcome assessments recorded in the database at the end 6-week PRP. The subjects in our study consisted of 23 patients (53.5%) with a diagnosis of iPAH, 13 patients (30.2%) had PAH associated with CHD, and 7 patients (16.3%) had PAH associated with scleroderma (Ssc). The mean time from diagnosis to initiation of pulmonary rehabilitation program was 1.4 ± 2.2 (mean ± SD) years.

Demographic data, diagnosis, hemodynamics, functional class, and 6-minute walking distance values are summarized in Table 4. At the time of enrollment into the pulmonary rehabilitation program (assessment phase)

our sample represented a severely compromised PAH patient group with limited exercise capacity defined by the following baseline characteristics: patients were WHO FC III (n =32) or IV (n = 11), the mean baseline 6MWD was 320.7m ±111.3m (mean ± SD), mean mPAP (mmHg) was 62 ±15.9 (mean ± SD), mean RAP (mmHG) 11.0 ± 4.0 (mean ± SD), PVR (dynes.sec.cm-5) 899.9 ±377.6 (mean ± SD), and mean CI ($L.min^{-1}.m^{-2}$) 2.7 ±0.73 (mean ± SD). PAH treatment at baseline consisted of 90.7% of patients on combination therapy, defined as 2 or more PAH treatments from different therapeutic classes of PAH targeted therapies. (53.5% of the patients were on a combination of 3 PAH targeted treatments) All 42 patients that completed the 6-week PRP remained on the same PAH treatment regimen that they was recorded at the assessment phase of the 6-week PRP.

Table 4: Baseline Demographic and other Characteristics of Study Patients

Variable	Statistic
n	43
Male, count (%)	16 (37.2)
Age in years, mean (SD)	43.1 (13.6)
PAH Diagnosis	
iPAH (%)	23 (53.5)
CHD-PAH	13 (30.2)
Ssc-PAH	7 (16.3)
Right Heart Catheterization, mean (SD):	
mPAP (mmHG),	62.0(15.9)
RAP (mmHg)	11.0 (4.0)
CO (L/min)	4.6 (1.3)
CI ($L.min^{-1}.m^{-2}$)	2.7 (0.73)
PVR (dynes.sec.cm-5)	899.9 (377.6)
PAH Treatment, n (%)	
Endothelin Receptor Antagonist (ERA)	2 (4.7)
Prostanoid (PG)	1 (2.3)
ERA and PDE5i	13 (30.2)
ERA and PG	3 (7.0)
ERA and PDE5i and PG	23 (53.5)
No treatment	1 (2.3)
WHO Functional Class (WHO-FC),n (%)	
FC-III	32 (74.4)
FC-IV	11 (25.6)
Baseline 6 MWD	
mean (SD)	320.7 (111.3)
Time from diagnosis to start of the intervention (years)	
mean (SD)	1.4 (2.2)

3.2 Functional Assessments

3.2.1 Six-Minute Walk Test

There were 42 patients that completed the 6-week PRP and had 6MWD measurements at beginning and end of the six-week pulmonary rehabilitation program. The mean baseline 6MWD [323.7m ± 110.8 (mean ± SD)] demonstrated this cohort had an impaired exercise capacity, similar to other PAH studies with severe PAH patient subjects (33,34). After completion of the 6-week PRP program the mean increase in 6MWD was +7.4m (95% CI; -6.7, 21.6, p=0.293). This was not a significant change from baseline to post-treatment. Results for the 6MWD still remained non-significant after the change in distance was adjusted for sex, age, diagnosis, hemodynamics, and WHO FC (see Table 6).

Individual 6MWD for each individual patient are reported in Figure 1. Individual study subject's change in 6MWD identified a group (n=21) of '*responders'* (6MWD increased) and *non-responders* (n=21) (6MWD decreased or remained the same) at the end of the program (Figure 3). Grunig et al. (10) reported in their study assessing functional outcomes after PRP "responders" and "non-responders" based on 6MWD outcomes.

Table 5: Comparison of main outcomes before and after the 6-Week PRP in the study patients

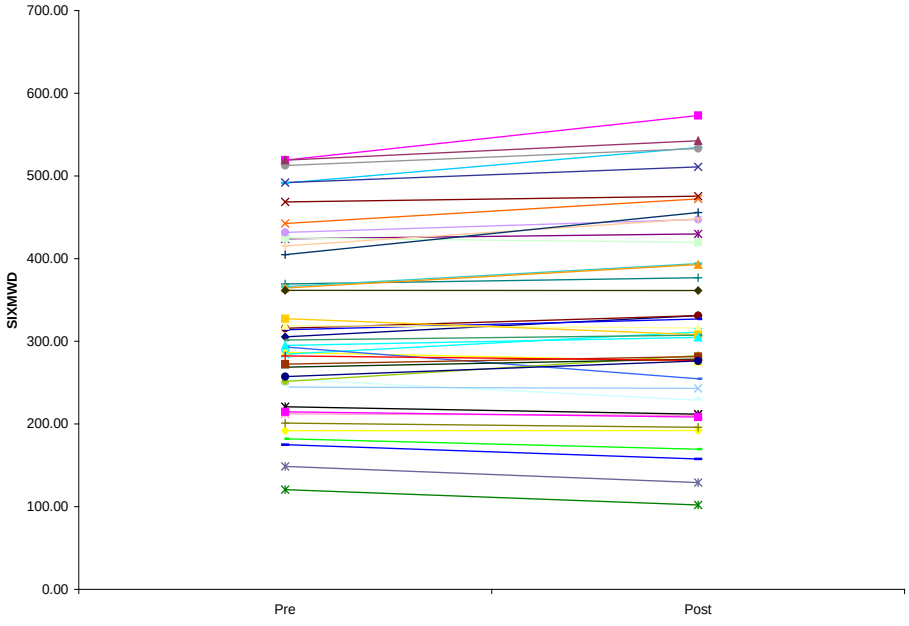
	Pre intervention (n=42)	Post intervention (n=42)	Difference (95% CI)	p-value
6MWD				
mean (SD)	323.7 (110.8)	331.1 (124.8)	7.4 (-6.7, 21.6)	0.293
BORG Scores				
mean (SD)	6.1 (2.2)	6.0 (2.6)	-0.1 (-0.6, 0.5)	0.787
median (IQR[1])	6 (4)	6 (4.25)		0.59
SF-36 Scores – Total and Individual (8) domains				
Total Score				
mean (SD)	345.2 (126.6)	453.2 (138.8)	108 (61, 155.1)	< 0.001
median (IQR)	328 (168.5)	452.5 (179.25)		< 0.001
Role Physical				
mean (SD)	31.2 (34.7)	50.7 (37.4)	19.5 (5.4, 33.5)	0.008
median (IQR)	20 (50)	52.5 (70.25)		0.011
Physical Functioning				
mean (SD)	23.1 (17.4)	42.2 (29.4)	19.1 (10.2, 28.0)	< 0.001
median (IQR)	20 (21.25)	47.5 (43.5)		< 0.001
Bodily Pain				
mean (SD)	57.3 (30.1)	58.9 (25.0)	1.6 (-7.7, 10.9)	0.731
median (IQR)	51.5 (53)	61.5 (31.25)		0.592
General Health Perception				
mean (SD)	28.6 (16.1)	40.8 (22.4)	12.2 (6.5, 17.9)	< 0.001
median (IQR)	25 (20.5)	41 (40)		< 0.001
Energy/Vitality				
mean (SD)	32.9 (24.5)	51.8 (22.3)	18.9 (12.1, 25.6)	< 0.001
median (IQR)	30 (30)	50 (31.25)		< 0.001
Social Functioning				
mean (SD)	46.3 (28.1)	57.3 (28.2)	11.0 (-0.03, 22.0)	0.051
median (IQR)	50 (38.25)	50 (38.25)		0.046
Mental Health				
mean (SD)	61.4 (21.7)	71 (17.8)	9.6 (4.1, 15.1)	0.001
median (IQR)	63 (27)	70 (27.25)		0.001
Role Emotional				
mean (SD)	65.5 (40.0)	85.6 (26.2)	20.1 (8.0, 32.3)	0.002
median (IQR)	100 (67)	100 (26.25)		0.002

Table 5 (cont'd): Comparison of main outcomes before and after the 6-Week PRP in the study patients

Chronic Respiratory Questionnaire – Summary and individual (4) domains				
Total Score				
mean (SD)	4.0 (1.1)	4.6 (1.2)	0.6 (0.3, 0.9)	0.001
median (IQR)	3.75 (1.625)	4.45 (1.95)		< 0.001
Dyspnea				
mean (SD)	3.3 (1.1)	4.0 (1.2)	0.7 (0.4, 1.1)	< 0.001
median (IQR)	3.2 (1.2)	3.6 (2.2)		< 0.001
Emotional Function				
mean (SD)	4.3 (1.2)	4.8 (1.2)	0.5 (0.2, 0.8)	0.003
median (IQR)	4.1 (2.0)	4.75 (2.0)		0.001
Fatigue				
mean (SD)	3.3 (1.3)	4.1 (1.2)	0.8 (0.4, 1.1)	< 0.001
median (IQR)	3.2 (2.0)	4.0 (1.6)		< 0.001
Mastery				
mean (SD)	4.5 (1.4)	5.1 (1.4)	0.6 (0.3, 0.9)	0.001
median (IQR)	4.3 (2.0)	5.2 (2.4)		< 0.001

[1] Inter quartile range

Figure 1: Fitted line for six minute walking distance (6MWD) for each study subject



3.2.2 Borg Dyspnea Scale

The Borg Dyspnea Scale (62), used to evaluate the perceived level of exertion, was assessed in all patients after completing the 6MWD, at the assessment phase and after completion of the six-week pulmonary rehabilitation program. Borg results are summarized in Table 5. The mean baseline score of 6.1 (2.2) in our patients studied reflects a strong to very strong individual perceived level of exertion after an activity (62), demonstrating this patient sample was severely compromised in their ability to perform physical activity. Upon completion of the six-week pulmonary rehabilitation program the mean BORG score decreased -0.1 (95% CI; -0.6, 0.5 p=0.787). This change was not significant (p>0.05) and remained non-significant after the average change was adjusted for sex, age, diagnosis, hemodynamics, and FC.

3.3 Health Related Quality of Life (HRQL) Assessments

In our protocol, 2 HRQL assessment tools were used to measure the patients perceived burden of disease: Short Form 36-Item Health Survey (SF-36) and Chronic Respiratory Questionnaire (CRQ). All 42 patients completed both assessment tools before and after the 6-week pulmonary rehabilitation program; scores are reported in Table 5. Not surprisingly, baseline SF-36 scores in our patient sample demonstrated significantly compromised quality of life scores compared with the normative Canadian population(63), and in 3 of the 4 physical component scales (role physical, physical functioning,

general health perception) showed a >60% score reduction in these scales (See Figure 2). After the 6-week pulmonary rehabilitation program, the mean change in the total SF-36 score and the mean scores for 6 of the 8 individual domains showed a significant improvement ($p<0.05$) for the study subjects (see Table 5). The improvements observed in all 6 of the 8 scales were representative of clinically important differences (CID) that have been reported for patients with chronic lung diseases(64,65).

Table 5 reports the mean scores in our study at baseline and at the end of the 6-week pulmonary rehabilitation program for the individual CRQ domains (dyspnea, emotional function, fatigue, and mastery). We observed significant improvements for each domain of the CRQ (See table 5). A change of 0.5 points is the reported MCID for each of the 4 domains of the CRQ(66). The mean change in each of the domains exceeded the MCID (>0.5 points) following the 6-week pulmonary rehabilitation program (see Table 5). After adjustment for sex, age, PAH diagnosis, hemodynamics, and FC the improvement in scores in the SF-36 and CRQ outcomes remained significant at the end of the program (see Table 6).

Table 6: Adjusted[2] average change in main outcomes post intervention in the study patients

	Adjusted coefficient (95% CI)	p-value
Six MWD	7.4 (-6.4, 21.1)	0.293
BORG	-0.10 (-0.64, 0.44)	0.71
	SF 36 Scores – Total and Individual (8) domains	
Total Score	117.2 (69.8, 164.5)	< 0.001
Role Physical	22.0 (8.4, 35.6)	0.002
Physical Functioning	20.2 (11.3, 29.0)	< 0.001
Bodily Pain	3.9 (-5.3, 13.1)	0.409
General Health Perception	13.3 (7.6, 19.0)	< 0.001
Energy/Vitality	19.4 (12.7, 26.1)	< 0.001
Social Functioning	12.8 (1.7, 23.8)	0.024
Mental Health	8.7 (3.7, 13.6)	0.001
Role Emotional	21.1 (8.6, 33.6)	0.001
Chronic Respiratory Questionnaire – Summary and individual (4) domains		
Total Score	0.63 (0.32, 0.93)	< 0.001
Dyspnea	0.74 (0.38, 1.10)	< 0.001
Emotional Function	0.55 (0.25, 0.85)	< 0.001
Fatigue	0.75 (0.36, 1.1)	< 0.001
Mastery	0.64 (0.33, 0.96)	< 0.001

[2]Adjusted for sex, age, PAH diagnosis, 6MWD, mPAP, RAP,CO, CI, pvr, PAH treatment, WHO FC baseline using random effects models

Figure 2: Mean SF-36 scores at baseline and after the 6 week PRP compared to the Canadian Normative Population(63)

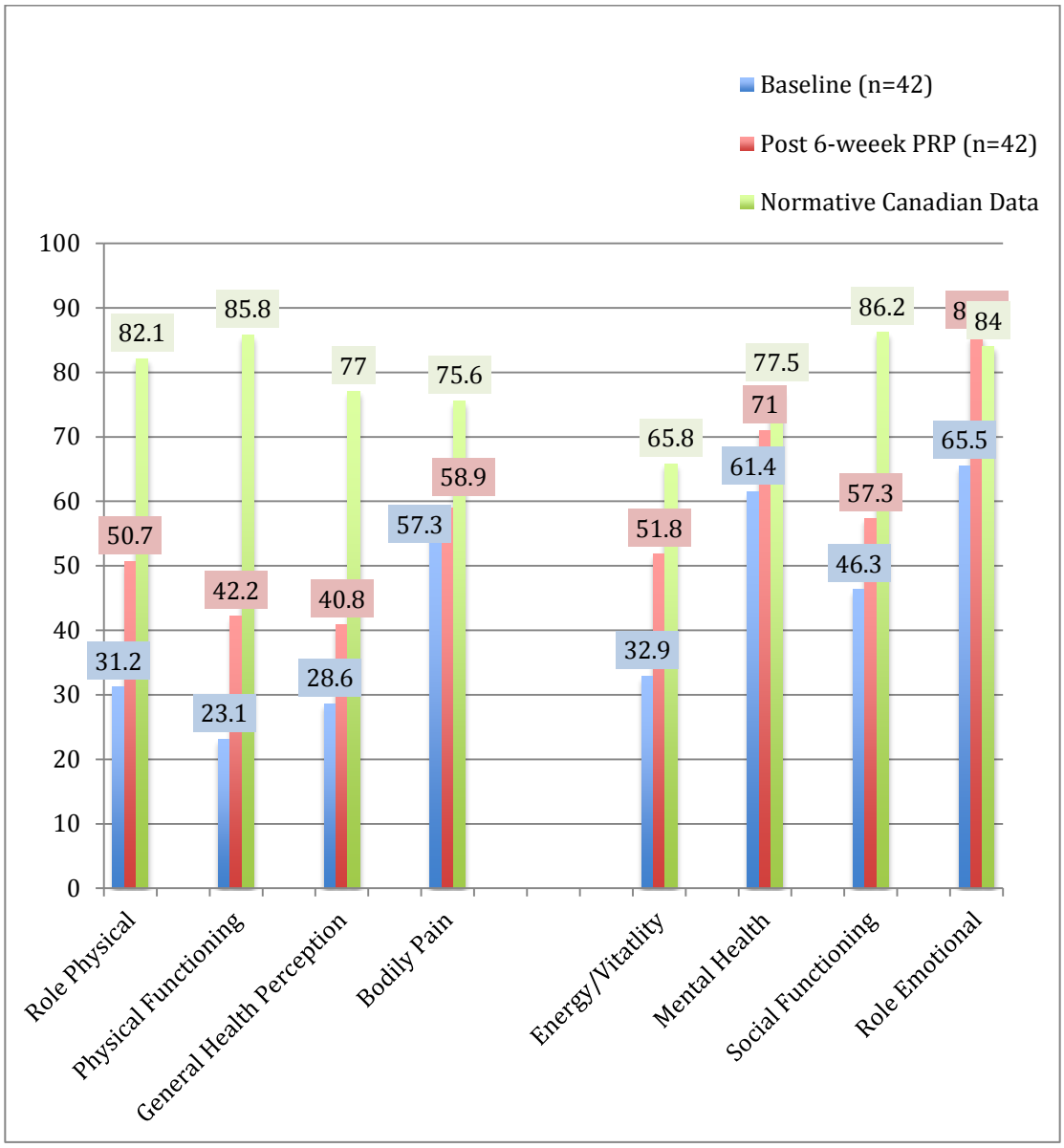


Figure 2: Mean SF-36 scores improved for 6 of the 8 scales – Role Physical, Physical Functioning, General Health Perceptions, Energy/Vitality, Mental Health, and Role Emotional. The respective values for the Normative Canadian Population (n=9423) (53) are shown for comparison.

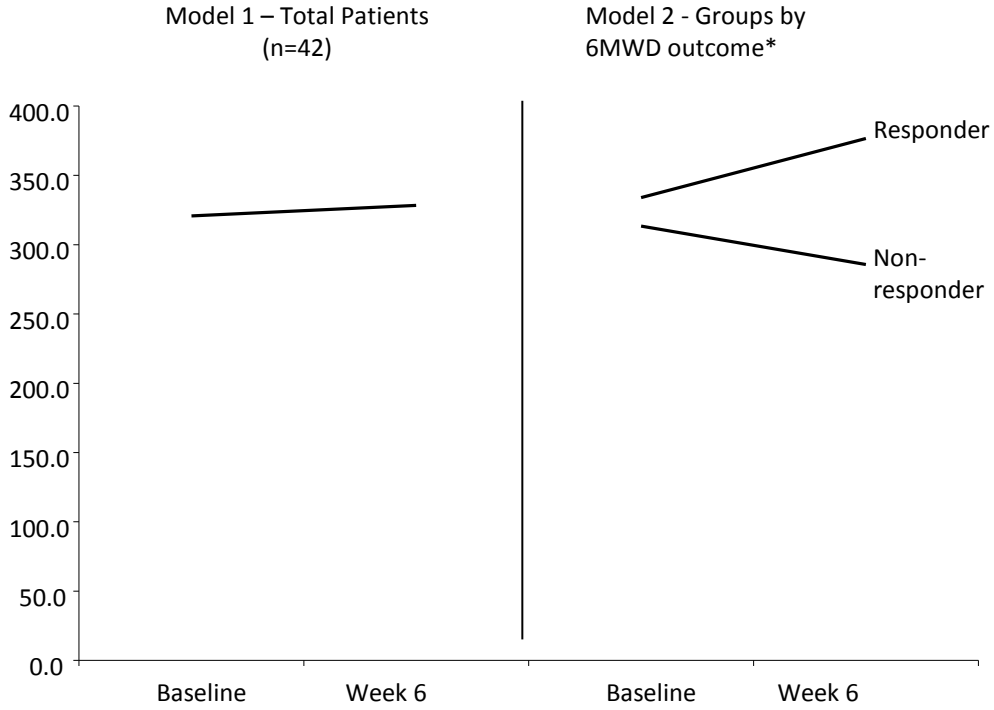
3.4 Safety

The safety assessment for the six-week pulmonary rehabilitation program in our cohort consisted of any of the following adverse events reported during participation: death, hospitalization, withdrawal from the program because of disease worsening, and symptoms during exercise (syncope, arrhythmias, acute RHF, ER visits, MI) requiring stoppage during the exercise session. All 42 patients that initiated the six-week program completed the program. There were no deaths, hospitalizations, withdrawals due to disease worsening, or any reported symptoms during exercise during the patients' participation in the 6 -week programs.

3.5 Subgroup Analysis

A subgroup analysis was conducted to explore the data by dividing the study patients into 2 groups; *responders* (increase in 6MWD after six week pulmonary rehabilitation program participation) and *non-responders* (no change or decrease in 6MWD after six week pulmonary rehabilitation program participation). The 6MWD results after dividing the study patients into these 2 groups are presented in Figure 3 and Table 7. The *responder* patients (n=21) had a significant mean increase in 6MWD from baseline of +42.67m (SD 29.7, $p<0.001$) at the end of the 6-week. The *non-responder* patients (n=21) had a significant mean decrease from baseline in 6MWD of -27.76m (SD 27.0, $p<0.001$).

Figure 3: Average within subject change in six minute walking distance post 6 week Pulmonary Rehabilitation Program



* Study patients grouped in Model 2 based on 6MWD outcome at the end of the 6-week PRP. *Responders* (subjects for whom walking distance increased) and *non-responders* (subjects for whom walking distance remained the same or decreased)

Table 7: Change in six minute walking distance after the 6-week Pulmonary Rehabilitation Program

Type	Mean (SD)	p-value
Responder (Subjects for whom walking distance increased) (N=21)	42.67 (29.7)	< 0.001
Non-Responder (Subjects for whom walking distance decreased or remained same) (N=21)	- 27.76(27.0)	< 0.001
Overall (N=42)	7.45 (45.34)	0.293

Mean changes after the 6-week pulmonary rehabilitation program for the BORG scale and the HRQL assessment tools (SF-36 and CRQ) in these 2 subgroups were examined using paired t-tests. The mean change in the BORG scale after the 6-week PRP for both subgroups were non-significant (See Table 8). Comparing HRQL assessments between the 'responder' (n = 21) and 'non-responder' (n = 21) subgroups (see Table 8) saw a significant improvement ($p<0.05$) after the 6-week pulmonary rehabilitation program the Total SF-36 score for both groups, and mean scores significantly ($p<0.05$) improved for 7 of the 8 individual SF-36 domains in the *responder* subgroup but only 3 of the 8 individual domains in the 'non-responder' group significantly ($p<0.05$) improved.

The improvements in the 7 domains of the SF-36 in the responder group were >10 points each and these changes would represent a CID for the SF-36 in patients with chronic lung diseases (64,65). The *responder* group also achieved a significant improvement in each of the CRQ domains (see Table 8) which also represent a CID (66). The non-responder had a significant ($p<0.05$) improvement at the end of the 6-week pulmonary rehabilitation program in 3 of the 8 SF-36 individual domains, but the 4 CRQ domains did not reach statistical significance and in three of the 4 domains (emotional, fatigue, and mastery) the change observed in each was smaller than the defined CID for the CRQ (see Table 8) (66).

Table 8: Change in QOL in study patients after the intervention stratified by change in six minute walking distance

	Non-Responder Group		Responder Group	
	Mean change (SD)	p-value	Mean change (SD)	p-value
BORG	0.24 (1.95)	0.581	-0.38 (1.39)	0.225
SF 36 Scores – Total and Individual (8) domains				
Total Score	110.71 (174.55)	0.009	105.33 (127.58)	0.001
Role Emotional	15.57 (39.37)	0.085	24.71 (38.98)	0.009
General Health Perception	10.95 (18.78)	0.015	13.43 (18.14)	0.003
Mental Health	9.10 (20.42)	0.055	10.05 (14.86)	0.006
Bodily Pain	10.76 (29.36)	0.109	-7.57 (28.12)	0.232
Physical Functioning	17.62 (24.01)	0.003	20.57 (33.12)	0.010
Role Physical	16.19 (42.53)	0.096	22.76 (48.26)	0.043
Social Functioning	7.76 (42.54)	0.413	14.19 (26.97)	0.026
Energy/Vitality	21.33 (21.73)	< .001	16.43 (21.86)	0.003
Chronic Respiratory Questionnaire – Summary and individual (4) domains				
Total Score	0.49 (1.21)	0.077	0.64 (0.75)	0.001
Dyspnea	0.51 (1.28)	0.082	0.99 (0.93)	<0.001
Emotional Function	0.47 (1.29)	0.109	0.54 (0.70)	0.002
Fatigue	0.35 (1.06)	0.142	1.16 (1.31)	0.001
Mastery	0.31 (1.23)	0.257	0.89 (0.76)	< 0.001

Additional analyses on the 2 subgroups (*responder/non-responder*) were conducted. Baseline characteristics between the 2 subgroups were compared and results are presented in Table 9. At baseline the *responder* subgroup had better cardiac function versus the *non-responder* subgroup, demonstrated by a significantly higher cardiac output (5.09mmHg (SD 1.59) versus 4.22mmHg (SD 0.90) respectively, p =0.035) and cardiac index (2.93 (SD 0.77) versus 2.47 (SD 0.62) respectively, p= 0.039). Another difference at baseline was a significant higher number of patients (18 versus 3, p=0.004) improved their 6WMD when on more aggressive treatment regimens than those patients who were on less aggressive treatment regimens.

To study characteristics that potentially influence the improvement in 6MWD a fitted logistic regression analyses of the 6MWD (yes=1; decreased or remained the same = 0) with a selected list of variables (see methods for list of variables) was used. In the univariable regressions model cardiac function (CO, CI), PAH treatment, and diagnosis (CHD-PAH) were variables found to be significant ($p<0.20$); increasing or decreasing the likelihood of having a improved 6MWD after the 6-week PRP (see Table 10). The variables that were significant from this model were considered candidates for the multivariable model. The results of the multivariable model are presented in Table 11. Only cardiac output had a statistically significant (p=0.024) contribution in the analysis, having an adjusted odds ratio of 6.35 (1.27,

31.81, 95% CI). This indicated patients who had a cardiac output >4.3 L/min at baseline were over 6 times more likely to have an increase in 6MWD after completing the 6-week PRP. A scatter plot lowess line analysis showed the relationship between cardiac output and 6MWD response (Figure 4). From the multivariate regression analysis and the lowess line scatter plot, having a higher cardiac output was associated with a greater likelihood of having an increase in 6MWD after completing the 6-week pulmonary rehabilitation program.

Table 9: Baseline demographic and characteristics of study patients stratified by change in six minute walking distance

	Six minute walking distance after the intervention		
	Decreased or remain same (N=21)	Increased (N=21)	p-value
Male, count (%)	9 (42.9)	7 (33.3)	0.751
Age in years, mean (SD)	42.5 (14.9)	44.2 (12.6)	0.703
mPAP (mmHG), mean (SD)	61.7 (14.0)	61.7 (18.2)	1
RAP (mmHG), mean (SD)	11.0 (4.2)	10.9 (4.1)	0.911
PVR (dynes.sec.cm-5), mean (SD)	957.3 (347.4) (n=20)	839.4(407.5) (n=19)	0.336
CO (L/min), mean (SD)	4.22 (0.90)	5.09(1.59)	0.035
CI ($L.min^{-1}.m^{-2}$), mean (SD)	2.47 (0.62)	2.93 (0.77)	0.039
PAH Treatment			
ERA, or ERA & PG, or ERA, PG & PDE5i	9 (42.9)	18 (85.7)	0.004
PG, or ERA & PDE5i, or no treatment	12 (57.1)	3 (14.3)	
Diagnosis			
iPAH	9 (42.9)	13 (61.9)	0.055
CHD-PAH	10 (47.6)	3 (14.3)	
Ssc_PAH	2 (9.5)	5 (23.8)	
WHO-FC at baseline			
III	15 (71.4)	16 (76.2)	0.726
IV	6 (28.6)	5 (23.8)	

Table 10: Univariable logistic regression model of increment of six minute walking distance (Yes=1, 0=decreased or remained same)

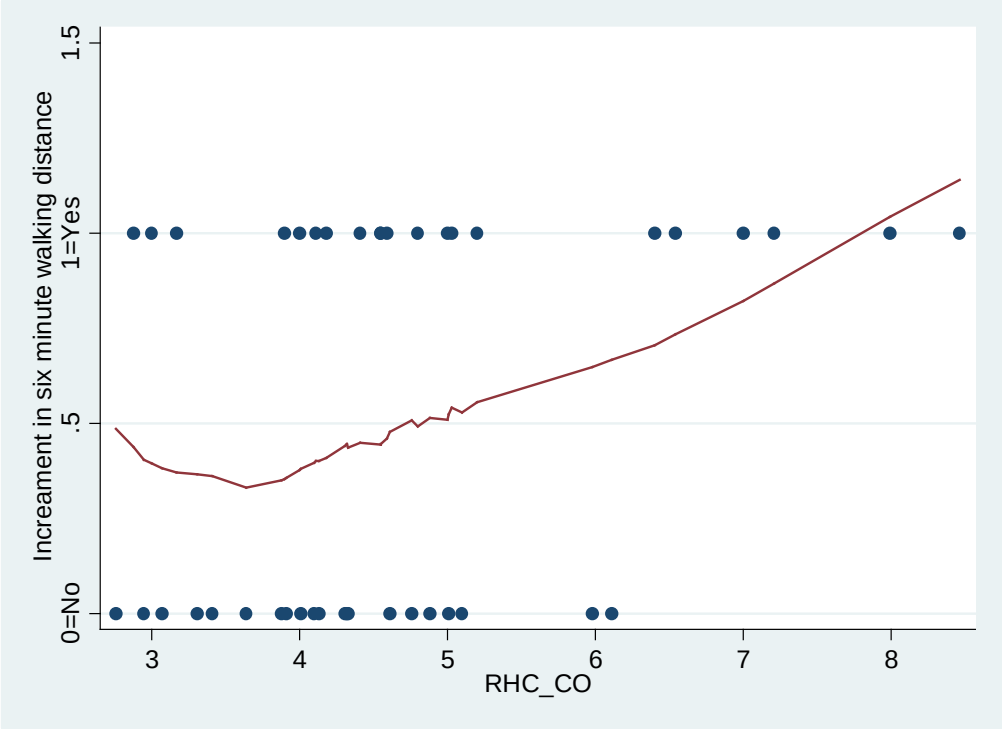
	OR (95% CI)	p-value
Cardiac Output (L/min), (CO)		
≤ 4.33	-	
> 4.33	4.00 (1.11, 14.43)	0.034
Cardiac Index ($L.min^{-1}.m^{-2}$), (CI)		
≤ 2.66	-	
> 2.66	4.00 (1.11, 14.43)	0.034
PAH Treatment		
PG, or ERA & PDE5i, or no treatment	-	
ERA or ERA & PG or ERA, PG & PDE5i	8.00 (1.79, 35.74)	0.006
Diagnosis		
iPAH	-	
CHD-PAH	0.21 (0.04, 0.97)	0.046
Ssc_PAH	1.73 (0.27, 10.97)	0.560

Table 11: Multivariable logistic regression model[3] of increment of six minute walking distance (Yes=1, 0=decreased or remained same)

	Adjusted OR (95% CI)	p-value
Cardiac Output (L/min), (CO)		
≤ 4.33	-	
> 4.33	6.35 (1.27, 31.81)	0.024
PAH Treatment		
PG, or ERA & PDE5i, or no treatment	-	
ERA or ERA & PG or ERA, PG & PDE5i	5.67 (0.85, 37.72)	0.073
Diagnosis		
iPAH	-	
CHD-PAH	0.29 (0.04, 2.13)	0.221
Ssc_PAH	1.02 (0.13, 8.10)	0.988

[3] The overall model is significant (LR χ^2 (4) = 15.66 with p-value = 0.0035). The model fits the data well (Hosmer-Lemeshow χ^2 (6) = 9.76 with p-value = 0.135; C-statistic=0.837).

Figure 4: A scatter plot of increment in six minute walking distance vs. RHC_CO with lowess line



Chapter IV: Discussion

4.1 Summary of Results

In our study we evaluated the efficacy and safety of pulmonary rehabilitation in adult patients (n=43) with severe PAH and marked to severe exercise limitations. Patients were enrolled in a 6-week pulmonary rehabilitation program at the University of Alberta Hospital Lung Transplant Program. During the 6 weeks, patients participated in supervised, in-hospital exercise sessions 5 days a week at the Department of Physical Therapy. Exercise sessions were individualized and consisted of: aerobic training, extremity and core strength training, balance training, stretching/flexibility activities and postural correction. Patient demographics, safety and outcome measures were collected before, throughout and after completion of the program.

At the initiation of the PR program all patients had marked to severe exercise limitations; were in WHO FC III (n=32) or IV (n=11) , had a baseline 6MWD of 320.7m ± 111.3 (mean ± sd), and had severe impairments in HRQL (see Table 5). Our study found pulmonary rehabilitation to be safe in this sample of patients, as all patients completed the 6-week program, with no reported adverse event(s) during participation. After completion of the 6-week program there was an overall +7.4m (95% CI [-6.7, 21.6]) improvement in the 6MWD from baseline. This improvement was not statistically significant. HRQL outcomes were assessed using the SF-36 and CRQ assessment tools.

Results for our sample of PAH patients demonstrated a significant ($p<0.05$) improvement in both HRQL instruments at the end of the program (see Table 5).

Further analysis showed distinct groups of *"responders"* and *"non-responders"* to PR based on the change in 6MWD at the end of the 6-week program (see Table 7). Logistic regression analysis was performed to evaluate which baseline characteristics were predictive of having an increase in 6MWD after participation in the 6-week PRP. Only cardiac output had a statistically significant ($p=0.024$) contribution in the analysis, having an adjusted odds ratio of 6.35 (1.27, 31.81, 95% CI). This indicated patients who had a cardiac output >4.3 L/min at baseline were over 6 times more likely to have an increase in 6MWD after completing the 6-week PRP.

This study demonstrated pulmonary rehabilitation was a safe adjunctive treatment option in patients with severe PAH, and improved exercise capacity and HRQL in patients with preserved cardiac function.

4.2 Study Subjects

Our study is the first study to look at the efficacy and safety of PR in a specific sample of patients with severe PAH, having marked to severe compromise in exercise capacity and severe cardiopulmonary limitations. Previous studies have primarily evaluated the efficacy and safety of PR in PAH patients with

stable disease and mild exercise limitations(6-10,54,55). Differences in our patient sample versus previous studies were: patients enrolled in previous studies had mild symptoms, functional status was primarily WHO FCII or III, and mean 6MWD was >400m. (7-10,55) Only one previous study included a proportion (>10%) of patients in WHO FC IV at baseline(6). Patient baseline characteristics in our study represented patients with severe exercise limitations. All patients were either WHO FCIII (n=32) or IV (n=11) and had a lower baseline 6MWD of 320.7m ± 111.3 (mean ± SD). Additionally, all patients in our study were on optimal pharmacological treatment for PAH; consisting of 2 or 3 PAH targeted therapies (37.2% of patients were on 2 PAH targeted pharmacological treatments and 53.5% were on 3 PAH targeted pharmacological treatments – see Table 4). Finally, all patients that participated in our PRP had been listed for lung transplant surgery; confirming these patients had severe and advanced PAH. Advanced stages of PAH increases the susceptibility of patients developing right ventricular failure that can occur as a manifestation of the disease or as a result of a triggering factor(s) (i.e. arrhythmia) (67). Careful management of these patients is important to assure right ventricular function is improved or reserved and interventions do not worsen right ventricular function. Our study provided important information on the outcomes and safety of PR in patients with severe PAH.

4.3 Safety of PR in a severely compromised PAH patients with limited exercise capacity

One of the primary goals of our study was to evaluate the safety and tolerability of PR in PAH patients with severe PAH and marked to severe exercise limitations. Previously PAH experts' opinion recommended against exercise in all PAH patients for concerns of worsening symptoms and/or worsening right heart failure(5). These concerns were based primarily on the understanding of pathophysiologic changes in the pulmonary vasculature that would impact the normal physiologic response to exercise. The severe pathophysiological changes in the pulmonary vasculature in advanced stages of PAH and the resulting altered physiological response to exercise, increase the risk of severe PAH patients having adverse events during exercise. Therefore, evaluating the safety of PR in these patients is pivotal in understanding the role of PR as an adjunctive treatment. In our study no patients had any adverse events associated with worsening of symptoms, or worsening of right heart failure, and all patients were able to complete the 6-week program. Our findings are similar to previous findings in PR studies in PAH patients with milder disease that reported no severe adverse events related to progression of symptoms, progression of PH, or worsening right heart failure(6,7,9,54). In all previous PR studies in PAH patients only a minimal number of minor events (i.e. fatigue and light dizziness) have been reported(8,10,55). Our results expand the safety and tolerability evidence

for PR to include patients with severe PAH and marked to severe physical activity limitations.

Our study safety results also provide important information regarding the type, duration, and intensity of the PRP that is safe and tolerable for patients with PAH and marked to severe physical activity limitations. A safe PRP for these patients would include a multi-disciplinary team with expertise in PAH and exercise sessions that are conducted in a well-controlled and supervised environment (i.e. in-hospital setting), to allow for close monitoring of the patient's health status during participation. Individualization of the program goals and exercise sessions should be determined by the patient's disease severity. Safe exercise sessions for severe PAH patients can include: aerobic training (i.e. treadmill and/or bicycle ergometry), extremity and core strength with free weights and resistive equipment, and balance, stretching, and flexibility activities. Exercise sessions should be incremental, low-intensity, and of short-moderate duration. The PR protocol in our study was consistent with the recommendations provided in recent guidelines that outline PRP composition(38,39). Therefore, current guidelines for PR may be appropriate to reference when designing a PRP for patients with severe PAH.

Our study was not able to evaluate long-term safety of PR, as the information collected from the database did not allow for this analysis. The long-term safety of PR in PAH is important to understand and the current information is

limited. To date only one study has provided information on the long-term safety of PR in PAH, having no safety concerns reported(55). Future research to evaluate the long-term safety of PR in PAH should be considered and would require a well-designed, long-term, prospective study with a control group for comparison to properly assess long-term safety concerns for PR in this patient group.

4.4 Efficacy of PR in severely compromised PAH patients with limited exercise capacity

4.4.1 Physical Function – 6MWD

Another primary goal of our study was to assess the outcomes of PR on physical function in patients with severe PAH. We used the 6MWT to measure the change in physical function and recorded patients' distance walked during the test at the beginning and end of the PRP. The 6MWD change from baseline at the end of the 6-week program in our study was a +7.4m (95% CI [-6.7, 21.6]) increase that was not statistically significant (p=0.293). This 6MWD increase was small compared to other studies in PAH patients, where reported 6MWD increases ranged from 32 to 96m between baseline and the end of the PRP(6-10,54,55). The mean baseline 6MWD [323.7m ± 110.8 (mean ± SD)] demonstrated this cohort had more limited exercise capacity compared to previous studies evaluating PR in PAH where the baseline 6MWD reported in these studies were mostly greater than 400m

(7-10,54,55) representing PAH patients with less impaired exercise capacity than our patients.

The severity of the pathophysiological changes, skeletal muscle dysfunction, and/or the duration of the PRP may have been the underlying cause(s) for our study patients not achieving a significant increase in physical function (i.e. improved 6MWD) after participation in the PRP.

In our study patients had severe limited exercise capacity at baseline that was demonstrated by a 6MWD of 320.7m ± 111.3 (mean ± SD) and a BORG score of 6.1±2.2 (mean ± SD). Baseline PVR was 899.9 dynes.sec.cm^{-5} ± 377.6 (mean ± SD) and mPAP was 62.0 mmHg ± 15.9 (mean ± SD) indicating severe underlying pulmonary vasculature remodeling. One of the underlying causes for severe exercise limitation in PAH is the pathophysiological changes in the pulmonary vasculature that limits the ability of the cardiorespiratory system to adequately meet the metabolic needs during exercise (67). These severe deficiencies in the cardiorespiratory system of our study patients may have limited the ability to achieve an adequate exercise intensity level required during exercise training to improve their exercise capacity.

In PAH cardiac output during exercise is impaired due to the increase in pulmonary arterial pressure (PAP) and the decreased left ventricular volume due to the enlarged right ventricle limiting diastolic filling(68). Pulmonary

vasculature remodeling decreases vasodilation and recruitment of unused vascular units to accommodate the increased blood flow during exercise causing reduced vascular capacitance(69). Decreased perfusion in the remodeled pulmonary artery bed results in a perfusion and ventilation mismatch that limits respiratory efficiency(69). Impaired cardiac output and reduced vascular capacitance lead to decreased oxygen delivery to exercising muscles that increases lactic acidosis by less efficient (anaerobic) energy metabolism(68). These changes in the physiologic response to exercise would decrease the amount of exercise performed before the patient experienced dyspnea and fatigue. Sun et al. (70) demonstrated there is a reduced peak oxygen consumption (peak VO2) and anaerobic threshold (AT) that occur at relatively low work rates (WR) in PAH patients. This would result in more work being done anaerobically. In this same study peak VO2 and AT correlated with the increasing severity of PAH(70), demonstrating PAH patients with severe disease, like those in our study, would experience anaerobic metabolism and muscle fatigue at a lower work rate than normal individuals and patients with milder PAH. These deficiencies in the cardiorespiratory system would have resulted in the inability to meet the metabolic demand during exercise and may have resulted in the inability of patients in our study to achieve an adequate intensity level required during the exercise program to improve their exercise capacity.

In further analysis the patients were divided into 2 groups based on their change in 6MWD after completion of the 6-week PRP. The 2 groups were designated as: *'responder'* or *'non-responder'.* The *'responder'* group was defined as any patient that had any improvement in their 6MWD after the 6-week PRP and the '*non-responder'* group was any patient that had no improvement or a decreased 6MWD after the 6-week PRP. The *'responder'* group (N=21) had a significant increase in 6MWD from baseline of +42.7m ± 29.7 (mean ± SD), whereas the *'non-responder'* group (N=21) had a significant decrease of -27.8m ± 27.0 (mean ± SD). Comparing the baseline characteristics between these 2 groups a significant difference was seen between: cardiac output, cardiac index, and PAH treatment (see table 9). Also worth mentioning was the difference in PVR values (>100 dynes.sec.cm^{-5}) (see table 9)) at baseline between these 2 groups because PVR provides information on severity of the disease and the degree of pulmonary vascular remodeling in the pulmonary vessels. However this difference did not reach statistical significance. The hemodynamic variables in the *'responder'* group demonstrated these patients had better cardiac function (i.e. CO and CI) and less pulmonary vascular disease (i.e. PVR). The *'responder'* groups' increase in 6MWD was similar to other results seen in PR studies in PAH and COPD(6-10,48-50,54,55). In previous PR studies in PAH where an improvement in 6MWD was seen the reported hemodynamics in these study patients were comparable or better than the responder group identified in our study. Our results provide information that indicate patients with a better-preserved

cardiac output (i.e, *'responder'* group) are more likely to have an increase in their physical function after participation in a PRP versus those patients lower cardiac output.

Logistic regression analyses were used in our study to evaluate which characteristics were predictive of having an increase in the 6MWD after participation in our 6-week PRP (see Table 10 and Table 11). Cardiac output was the only baseline characteristic found to be predictive ($p<0.05$) of determining which patients could be expected to have an improvement in 6MWD after completion of the 6-week PRP. In our study patients with a cardiac output of >4.33 had an odds ratio of 6.35 (95% CI [1.27,31.81]) for improving 6MWD after the 6-week PRP. Additionally the lowess line analysis (Figure 4) also demonstrated the relationship between a higher baseline cardiac output and the likelihood of improving 6MWD at the end of the 6-week PRP. These results identify cardiac output as a disease characteristic in PAH patients that may predict patients that may improve their 6MWD after participation in a PRP as adjunctive treatment. In the literature other studies have identified patients that do not see an improvement in functional capacity measures (i.e. 6MWD) after PR(9,10). Grunig et al. (10) categorized these patients as 'non-responders'. For COPD the reported non-responders range from ¼ to 1/3 of the patients participating in PR programs(71,72). In neither the COPD or PAH populations were the underlying criteria for nonresponse established.

Using our results and assessing the baseline cardiac output of patients with severe PAH may identify patients that would do well in a PR and improve their physical function after participating in a PRP. Baseline cardiac output could be used as an inclusion criterion to select which patients were eligible to participate in PRPs because of the increased likelihood of having a positive effect on physical function. Another alternative would be to use these findings to set treatment goals for patients with severe PAH when participating in PRPs. Knowing if patient were more or less likely to have an increase their 6MWD after participation would determine if an improvement in 6MWD was likely or if improving quality of life was a more realistic goal for some patients with severe PAH.

Lack of improvement in exercise capacity could have also been due to the duration of the PRP. The PRP evaluated in our study was 6 weeks in duration. In our study patients that had more physiologic and skeletal muscle dysfunction it may take a longer training duration to significantly stimulate and change the cardiorespiratory and skeletal muscle systems in order to reverse the deleterious effects. In COPD, a recent review (49) and position statement (38) stated longer rehabilitation programs provide better outcomes related to exercise capacity. In PR studies in PH patients where a significant change in 6MWD was demonstrated, all programs were between 12-15 weeks(7,8,10,54,55). To date there is no PR studies in PAH patients

assessing the impact on duration of the PRP on outcomes. Future research may consider evaluating the duration of the PRP in PAH patients to determine if it has any impact on the outcomes of physical function.

In our study skeletal muscle dysfunction was not evaluated. Recent research demonstrates skeletal muscle dysfunction contributes to the exercise limitations (i.e.6MWT) in patients with PAH (8,9,57). It has also been shown that PR has the ability to improve skeletal muscle dysfunction in PAH and may be a contributing factor to the improved physical function achieved with PR (8,9). Skeletal muscle dysfunction is improved as a result of changes to skeletal muscle biochemistry, morphology and muscle fiber types that result in better endurance, less fatigue, and a higher lactate threshold allowing for improved exercise capacity and tolerance (8,9). Changes to muscle function after PR have been reported and these changes are considered an underlying factor contributing to the improved exercise benefits achieved in COPD(4).

Our patients had severe PAH and greater exercise limitations based on the baseline 6MWD and hemodynamics. Based on evidence of intolerance to exercise associated with the severity of PAH(70) and evidence showing correlation between skeletal muscle abnormalities and the severity of disease and exercise capacity in PAH patients(57,58), it is possible that the exercise training program in our study may not have impacted exercise

pathophysiology and skeletal muscle performance to a significant enough level to improve exercise capacity.

Our study was not designed and did not have the ability to evaluate the effect of PR on exercise pathophysiology or skeletal muscle abnormalities, but future research analyzing these parameters in severe PAH patients may provide additional information to help define the benefits of PR for this group of PAH patients. Part of this research could incorporate CPET to assess the physiologic changes in exercise and understand the physiologic effects of PR on physical functioning in patients with PAH.

4.4.2 Health Related Quality of Life

In our study we assessed the effect of PR on HRQL in patients with severe PAH after a 6-week PRP using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the Chronic Respiratory Questionnaire (CRQ) instruments. The SF-36 is a validated generic health status questionnaire that includes 8 health concepts: role physical, physical functioning, general health perception, bodily pain, energy/vitality, social functioning, and role emotional (73). These 8 domains assess an individuals' perceived physical and mental health. The SF-36 has defined clinical important differences (CID) in chronic lung diseases (64,65), and has normative data available for Canada(63). To our knowledge at the time of

our study a CID for the SF-36 instrument has not been defined specifically for PAH patients. The CRQ is a validated disease-specific questionnaire used to assess quality of life in patients with chronic lung disease (74). The CRQ examines physical and mental aspects of chronic respiratory disease: dyspnea, fatigue, emotional function, and mastery (the feeling of control over the disease and its effects) (74). CID has also been defined for the CRQ in chronic lung diseases(66). Both of these instruments have been validated in chronic lung diseases, used to assess HRQL in patients with PAH, and have been endpoints in clinical studies to investigate the benefits of PR; making them appropriate instruments to investigate the potential benefit of PR in our sample of patients with severe PAH.

HRQL is becoming an important treatment goal in PAH because patients are now living longer due to the availability of effective pharmacological therapies(3,25,75,76). With PAH patients living longer it is increasingly important to understand the physical and psychological well-being and equally important to understand if adjunctive treatment options, like PRP impact HRQL in these patients. HRQL outcomes have been well studied for PR in COPD but to date only 3 studies(7,10,55) have evaluated HRQL outcomes for PRP in PAH patients with mild disease. In the 3 studies in PAH, PR has demonstrated the ability to improve HRQL(7,10,55). Our study investigated the potential benefits of PR in a sample of PAH patients with severe disease that has not previously been investigated.

Our study patients had severe PAH with severely depressed scores for every domain of the SF-36 survey compared to the normative population in Canada (see Figure 2). The depressed scores in all domains of the SF-36 demonstrate the overall burden PAH had on physical and emotional well-being in our patients studied. Taichmen et al.(77) previously evaluated HRQL in a PAH population with similar disease severity and reported the HRQL impairment in the PAH patient group studied was similar to other life-threatening conditions such as spinal cord injury, interstitial lung disease or cancer.

At the end of our 6-week PRP, individual SF-36 domain scores were significantly improved ($p<0.05$) in 6 of the 8 domains (see table 5). Each of the 4 CRQ domains were also significantly improved ($p<0.05$) at the end of the 6-week PRP (see table 5). The improvement in the 6 SF-36 domains were observed equally between the domains representative of physical and mental function; demonstrating PR has an ability to improve the physical and psychological well-being of patients with severe PAH. The significant improvement observed in all 4 of the CRQ domains further demonstrated the ability of PR to improve the physical and emotional aspects associated with PAH in our study patients.

To interpret the clinical relevance and significance of the statistically significant changes in the HRQL instruments scores in our study the change

in scores of the individual domains in both HRQL instruments were compared to defined clinically important differences (CID) reported for these instruments in chronic lung diseases. CID can be defined as the smallest difference in score in the outcome of interest that informed patients or health care provider perceive as important, either beneficial or harmful, and that would lead to a change in the management (66). CIDs are defined in the literature for the individual SF-36 domains in several chronic lung diseases. Currently the CIDs reported for the SF-36 instrument range from 3-4 points in patients with idiopathic pulmonary fibrosis (IPF) (65), to 10 to 40 points (classified as "small", "moderate' or "large") in patients with COPD(64). To date there are no published reports on the CID estimates for the SF-36 for PAH. CIDs have also been defined in the literature for the CRQ and a change of 0.5 points is the required change to meet the CID in each of the 4 domains (66).

Our results demonstrate that the significant improvements seen in the SF-36 individual domains are representative of a CID based on these definitions reported in the literature for chronic respiratory diseases. Table 5 reports the changes in the scores of the individual domains for the SF-36 survey at the end of the 6-week PRP. The improved scores in the 6 domains of SF-36 survey were significantly ($p<0.05$) improved, and improvements ranged from 12.2 (6.5, 17.9) [mean (95% CI)] to 20.1 (8.0, 32.3) [mean (95% CI)]. These scores are well above the defined CID of 3-4 points defined for

idiopathic pulmonary fibrosis (IPF) (65), and would be considered "moderate" CIDs from the defined CID in COPD (64). Table 5 also presents the changes in the individual CRQ domains in our sample at the end of the 6-week PRP. All 4 domains improved significantly ($p<0.05$) and the changes in all domains represented a CID, as individual domain scores increased ≥ 0.5 points (see Table 5), which is the defined CID for the CRQ (66). These changes demonstrated the ability of PR to provide a meaningful improvement to both physical and mental components of HRQL in our sample of patients with severe PAH. These improvements meet defined CIDs and therefore would be perceived as important to both the individual and the Health Care Provider.

Further analysis on HRQL outcomes was performed comparing outcomes between the *'responder'* (n=21) and *'non-responder'* (n=21) groups in our study (see Table 8). In the *'responder'* group the improvements in individual SF-36 domains were significant ($p<0.05$) for 7 of the 8 domains, and the improvements in the 4 individual CRQ domains were also significant ($p<0.05$). These observed improvements were of the same or higher magnitude than those seen in our overall sample of patients. In the *'non-responder'* group, only 3 of the individual 8 domains had significant ($p<0.05$) improvements after completion of the 6-week PRP (see table 5). The changes in the individual CRQ domains were not significant ($p>0.05$) and did not reach a magnitude to meet the defined CID (See Table 8). These findings

demonstrate that the *'non-responder'* group experienced a less significant impact on HRQL from participation in the 6 –week PRP compared to the *'responder'* group that saw a significant improvement in HRQL measurements that also met defined CIDs.

Findings from our analysis in the *'responder'* and *'non-responder'* sub-groups demonstrate that the *'responder'* group had an overall better response to PR than the *'non-responder'* group. The '*responder'* group had a significant improvement in 6MWD and significant improvement in HRQL outcomes that met CIDs for each of the instruments measured at the end of the 6-week PRP. The *'non-responder'* group did not see an improvement in 6MWD and did not have the same magnitude or significance of change in HRQL outcomes compared to the *'responder'* group. From the logistic regression analysis it was determined that cardiac output was the only baseline patient characteristic that influenced the outcome of the 6MWD after PR. Our results show that baseline cardiac output may be a valuable clinical tool to predict which patients with severe PAH may have a better outcome after participation in a PRP.

There are several limitations in our study. First, the results of our study are limited because of the retrospective design of our study and the sample subjects data collected from a database. The retrospective nature of the study did not allow for randomization or comparison to a control PAH group.

Additionally, the retrospective design did not allow for analysis of other measurements that assess cardiopulmonary function (i.e. cardiopulmonary exercise testing – CPET) during exercise that could have provided further information of our patients' exercise capacity and response to the participation in the 6-week PRP. This additional analysis may have provided more information to better understand the influence of hemodynamic baseline characteristics and outcome. The reason for this missing analysis was these tests were not performed at the time of our patients participation in the PRP.

Another limitation of our study could have been missing safety information not collected in the database because it was not defined in the data collections fields. Severe adverse events were collected in the database (death, hospitalization, withdrawn from program because of disease worsening) but symptoms during exercise (syncope, dizziness, chest pain, arrhythmias, acute right heart failure, emergency room visits, and hospital admissions) were only collected by the physiotherapist and entered into the patient medical records. If this information was not recorded in the medical records by the supervising physiotherapist during the patients participation in the 6-week PRP it would not be able to be accounted for in our analysis. Therefore symptoms during exercise may have been under-reported in our study. Since all 42 patients completed the 6-week program, overall safety and tolerance of exercise in this population is adequately confirmed as any

serious complications would have resulted in patient being withdrawal from the program.

The small number of patients meeting the inclusion criteria of our study is another limitation. Our study may have been underpowered to detect a significant change in physical and HRQL outcomes. However, it was our objective to exclusively study the safety and efficacy of PR in patients with more severe PAH than those groups previously studied and provide preliminary information in this group of patients.

Our findings provide preliminary information on the safety and efficacy of PR in PAH patients with severe disease and limited exercise capacity. Additional research is required to better understand the role of PR in this group. Future research may include; (1) CPET, to provide more descriptive evaluation of the cardiopulmonary function before and after PR in severe PAH patients, (2) skeletal muscle assessment, to assess baseline skeletal muscle dysfunction and response to PR in patients with severe PAH, (3) different PRP duration, to determine if the length of the program has an impact on the outcome, and finally (4) evaluation of baseline characteristics, to determine if there is underlying factors (i.e. cardiac output) that may identify which patients with severe PAH have a clinically significant response to PR.

4.5 Conclusion

Our retrospective study is the first study to provide preliminary information demonstrating the safety and efficacy of a 6-week PRP in a sample of PAH patients with severe disease and limited exercise capacity. Our study demonstrated the safety of PR as an adjunctive therapy in patients with severe PAH. All the patients in our study did not achieve improvements in exercise capacity and HRQL, but in those patients with preserved cardiac function (i.e. cardiac output) a clinically significant improvement in their exercise capacity and HRQL was observed. Larger randomized trials are needed to confirm these findings.

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