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Application of exercise testing in the diagnosis, prognosis, and treatment of patients with
Pulmonary Hypertension

Tesis Doctoral

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Six Minute Walk Test as a Substitute for the CardioPulmonary Exercise Test on the Pulmonary

Hypertension Population

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**“THE TRUE SIGN OF INTELLIGENCE IS NOT KNOWLEDGE BUT
IMAGINATION”**

**“EL VERDADERO SIGNO DE LA INTELIGENCIA NO ES EL CONOCIMIENTO,
SINO LA IMAGINACION” (EINSTEIN)**

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List of Publications

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List of Abbreviations

6MWD: Six Minute Walk Distance

6MWT: Six Minute Walk Test

ADLs : Activities of Daily Living

ANOVA: Analysis of Variance

AT: Anaerobic Threshold

ATP: Adenosine tri Phosphate

ATS: American Thoracic Society

BMI: Body Mass Index

bpm: beats per minute

cm: centimeters

CO: Cardiac Output

COPD: Chronic Obstructive Pulmonary Disease

CPET : Cardiopulmonary Exercise Test

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

ECG: Electrocardiogram

FDA: Food and Drug Administration

FEV1: Forced Expiratory Volume in one second

HR: Heart Rate

ICD: International Classification of Diseases

ICU: Intensive Care Unit

IPAH: Idiopathic Pulmonary Arterial Hypertension

IRB: Institutional Review Board

kg: kilograms

m: meters

max: maximum

MET: Metabolic Equivalent of Task

min: minute

ml: milliliters

mmHg: millimeters of mercury

mPAP: Mean Pulmonary Arterial Pressure

MVV: Maximum Voluntary Ventilation

PAH: Pulmonary Arterial Hypertension

PAP: Pulmonary Arterial Pressure

PETCO₂: Partial Pressure of End Tidal Carbon Dioxide

PETO₂: Partial Pressure of End Tidal Oxygen

PFT: Pulmonary Function Test

PH: Pulmonary Hypertension

PPH: Primary Pulmonary Hypertension

pVO₂: Peak Oxygen uptake

RER: Respiratory Exchange Ratio

RHC : Right Heart Catheterization

RPE: Rate of Perceived Exertion

RR: Respiratory Rate

s: seconds

SBP: Systolic Blood Pressure

SD: Standard Deviation

SpO₂: Peripheral Capillary Oxygen Saturation (measured via pulse oxymeter)

TV: Tidal Volume

VCO₂: Carbon Dioxide output

VE VO₂: Ventilatory equivalent for oxygen

VE/VCO₂: Ventilatory equivalent for carbon dioxide

VE: Ventilation

VO₂ max: Maximum oxygen uptake

VO₂: Oxygen Uptake

WHO: World Health Organization

RESUMEN

Introducción

En los últimos años las pruebas de esfuerzo así como el entrenamiento han venido a formar parte de la práctica clínica en el diagnóstico, tratamiento y pronóstico de la población enferma. Las pruebas de esfuerzo han sido utilizadas extensivamente en enfermedad cardiovascular así como en la enfermedad pulmonar. La prueba de máximo esfuerzo cardiopulmonar ha sido utilizada en el diagnóstico y pronóstico de pacientes con hipertensión pulmonar. Sin embargo, ningún estudio ha intentado evaluar la capacidad funcional, relacionar y predecir niveles de estado físico cardiopulmonar o la media de presión arterial pulmonar a partir de la prueba de marcha de seis minutos o a partir de la prueba de máximo esfuerzo cardiopulmonar.

Objetivos

Analizar y comparar diferentes grupos de edad de hipertensión pulmonar, explorar capacidad funcional y relación/predicción de resultados de salud a partir de pruebas de esfuerzo en forma de la prueba de marcha de seis minutos y la prueba de máximo esfuerzo cardiopulmonar, para evitar la realización de procedimientos invasivos y simplificar la vida de la población con hipertensión pulmonar.

Diseño de investigación

Los datos fueron recogidos como parte de las visitas clínicas al centro de hipertensión pulmonar del hospital infantil Morgan Stanley New York Presbyterian/Centro Médico de la Universidad de Columbia. El diseño y el protocolo del estudio incluye la prueba de marcha de seis minutos, la prueba de máximo esfuerzo cardiopulmonar, y en algunos casos un cateterismo de la parte

derecha del corazón. Las principales variables estudiadas fueron la distancia caminada en la prueba de marcha de seis minutos, el máximo consumo de oxígeno y otras variables espirométricas medidas en la prueba de esfuerzo, así como la media de presión arterial pulmonar.

Conclusiones

A). Las diferentes características de los diferentes grupos con Hipertensión Pulmonar fueron establecidas y comparadas con grupos normales. B). La capacidad funcional de los pacientes con hipertensión pulmonar fue establecida así como su comparación con sujetos sanos. Los sujetos con hipertensión pulmonar están severamente limitados en las actividades de la vida diaria y en especial cuando se comparan con sujetos sanos. C). El consumo máximo de oxígeno solo se puede predecir significativamente a partir de la prueba de marcha de seis minutos en niños con hipertensión pulmonar pero no en adolescentes o adultos con hipertensión pulmonar. D). La media de presión de la arteria pulmonar no se puede correlacionar o predecir a partir del consumo máximo de oxígeno o a partir de cualquier otro marcador de la prueba de máximo esfuerzo cardiopulmonar.

Palabras clave

Hipertensión pulmonar, prueba de marcha de seis minutos, Prueba de esfuerzo cardiopulmonar, consumo de oxígeno,

ABSTRACT

Background

Recent developments have added exercise testing and training as part of the clinical practice in the diagnosis, treatment, and prognosis of diseased populations. Exercise testing has been used widely in cardiovascular disease and in some circumstances in pulmonary disease. Cardiopulmonary Exercise Testing has been used in the diagnosis and prognosis of pulmonary hypertension patients. However, no many studies have tried to evaluate functional capacity, explore prediction of cardiopulmonary fitness levels or mean pulmonary arterial pressures from the six minute walk test and cardiopulmonary exercise testing.

Objectives

The objective of the study is to improve the quality of life of the pulmonary hypertension population with the use of exercise testing. Different pulmonary hypertension age groups have been analyzed and compared to achieve that goal. The functional capacity and prediction of health outcome from exercise testing in the form of six minute walk test and cardiopulmonary exercise test were explored to simplify the lives of this population, and to potentially avoid or decrease performing invasive procedures.

Research Design

The data was collected as part of the clinical visits to the pulmonary hypertension center of Morgan Stanley Children's Hospital of New York Presbyterian/Columbia University Medical Center. The design and protocol of the study involved six minute walk testing, cardiopulmonary exercise testing and in some cases right heart catheterization. The main variables in the study

were the distance walked in six minutes, the peak oxygen uptake and other gas exchange exercise markers, as well as mean Pulmonary Arterial Pressures via right heart catheterization (measured close to the date of exercise test).

Main Outcomes

A). The different demographic and exercise characteristics of different Pulmonary Hypertension groups and how they compare to normal groups were established. B). The functional capacity of subjects with Pulmonary Hypertension and how it compares to the functional capacity of healthy subjects was established. Subjects with Pulmonary Hypertension were severely limited in their activities of daily living, when compared to normal healthy subjects. C). Peak oxygen uptake could only be significantly predicted from the six minute walk test in children with PH but not in adolescents or adults. D). There did not seem to be a correlation between oxygen uptake or any other cardiopulmonary exercise testing markers and mean Pulmonary Arterial Pressures.

Keywords

Pulmonary Hypertension, Six minute walk test, Cardiopulmonary Exercise Test, Oxygen uptake,

1. INTRODUCTION

1.1. Evaluation of physical condition

1.1.1. General evaluation of physical condition

The benefits of a physically active lifestyle are widely known (Medicine, Swain, & Brawner, 2012). To determine what adaptations occur with physical activity a desire to measure, assess, and evaluate physical condition by measuring physical activity has been created. We live in an era of big data, where everything is measured and physical activity is not an exception. Physical activity is defined as “bodily movement generated by skeletal muscles resulting in energy expenditure” (Medicine, et al., 2012). It can be divided into two categories spontaneous physical activity and voluntary physical activity. When measuring physical activity we also have the ability to investigate the direct relationship between physical activity and disease endpoints as well as the indirect relationship with disease through the effects of body weight and diet (Medicine, et al., 2012).

Once physical activity is measured and assessed a physical capacity is established. Physical capacity can be evaluated at the general level and at the clinical level. Using exercise testing in the clinical evaluation of certain patient groups or diseases has become a very important tool in recent years.

Physical activity is objectively assessed by an instrument and evaluated by an individual's interpretation. Physical fitness is defined as the measurement of physical activity. The best way to measure physical fitness is by measuring cardiorespiratory fitness through exercise testing. Exercise testing is also performed to determine effectiveness of a preventative or rehabilitative fitness program, to develop exercise prescription or recommendations for return to work after an

injury or cardiac event, to determine level of health related physical fitness, to motivate an individual to establish goals, and to classify cardiovascular risk. (Pescatello & American College of Sports, 2014). In clinical practice there are three main indications for exercise testing: diagnosis, prognosis, and evaluation of functional capacity.

1.1.2. Exercise Testing

Exercise causes many physiological changes to increase energy output. This energy is obtained from the oxidation of metabolic substrate, which requires oxygen. Thus oxygen delivery to the cell is vital. During exercise there exists a higher demand for energy and as a consequence a higher demand for oxygen. Energy is obtained from the release of Phosphate (P) from Adenosine tri phosphate (ATP). The regeneration of ATP is obtained by three different mechanisms: anaerobic hydrolysis of creatine phosphate (PCr), aerobic oxidation of metabolic substrate (glycogen and fatty acids primarily), and anaerobic oxidation of glycogen or glucose by pyruvate. The aerobic oxidation of glycogen is the mechanism that yields most of the energy in steady-state submaximal exercise. During exercise testing oxygen uptake (VO_2) and carbon dioxide output (VCO_2) can be measured along with other measurements to evaluate exercise capacity and to determine substrate utilization. There are different modalities and protocols of exercise testing (McArdle, Katch, & Katch, 2001).

1.1.3. Exercise Testing Modalities and Protocols

1.1.3.1. Field Exercise Tests

Some exercise tests can be performed in the field without having to be confined in an exercise laboratory. Most of these tests measure exercise and functional capacity. Some of these tests used are:

- Stair climbing: test where the time required climbing a staircase of usually 10 stairs is measured. It is used in mobility limited older adults;
- Timed walk test (such as the six minute walk test): test where the maximum distance covered in an established period of time is measured;
- Shuttle walk test: test that measures how far and fast a subject can walk between objects that are 10 meters apart following signals that speed up until subject is unable to maintain speed (Holland et al., 2014).

The most common and used field test is the six minute walk test (6MWT).

1.1.3.2. Laboratory Exercise Tests

More complete and comprehensive exercise testing must be performed in an exercise laboratory. Laboratory exercise tests allow a more complete and safe analysis than field tests. There are three types of exercise modes depending on the measurement of work or energy (ergometry) used: treadmill, cycle ergometer, and arm ergometer.

Treadmill, the most common ergometry method, is used in individuals who can walk or run and it elicits higher work rates than the cycle or arm ergometer. Cycle ergometry is also widely used, especially in individuals with obesity, orthopedic issues, peripheral vascular, and/or neurologic

limitations. Arm ergometer is used in those subjects with lower extremity impairment (Pina et al., 1995).

There are many different exercise protocols depending on the exercise modality and desired increase in work-rate. The different protocols have (1-3 minute) stages with progressive increase in workload (speed and grade in treadmill or resistance in cycle and arm ergometer) on a step or ramping manner until maximum levels are achieved. The most widely used modes are performed on a treadmill. The Bruce protocol is the most popular protocol while the Naughton, Balke , or Cornell protocols are used in elderly populations. The different protocols are shown in table 1.

Table 1. Estimated Oxygen Cost of Bicycle Ergometer and Selected Treadmill Protocols.

From (Khoshdel, Mirzababaie, & Angoorani, 2014)

Functional Class	Clinical Status	O ₂ Cost ml/kg/min	METs	Bicycle Ergometer	Treadmill Protocols											
Normal and I	Healthy dependent on age, activity			1 watt = 6 kpds	Bruce	Cornell	Balke-Ware	ACIP	mACIP	Naughton	Weber					
				3-min stages								2-min stages	% grad all 3.3 mph	2-min stages First 2 stages 1 min	2-min stages	2-min stages
				MPH	%GR											
				5.5	20											
				For 70 kg body weight												
					MPH	%GR										
				5.0	18	5.0	18									
				KPDs												
				1500												
				1350												
				1200												
				1050												
				900												
				750												
				II	Sedentary healthy			600								
450																
300																
150																
III	Limited Symptomatic															
IV																

The standard Bruce protocol starts at 1.7 mph and 10 percent grade (5 METs), with larger increments between stages compared to other protocols such as the Naughton, ACIP, and Weber, which start at less than 2 METs at 2 mph and increase by 1- to 1.5-MET increments between

stages. The Bruce protocol can be modified by two 3-minute warm-up stages at 1.7mph and zero percent grade and 1.7 mph and five percent grade. METs = metabolic equivalents.

Some of these exercise tests are used in conjunction with other clinical diagnostic tests, such as heart imaging via echocardiography (using sonogram or ultrasound images) and nuclear stress test (using cardiac radionuclide imaging). Pharmacologic agents (such as adenosine, dobutamine, etc.) are also used to increase heart rate. This is a way of stressing the system in patients who cannot exercise.

The most common used graded exercise tests are the treadmill echocardiogram and the nuclear stress test. The treadmill echocardiogram stress test involves echocardiographic images of the heart before and immediately after a graded exercise on a treadmill (or sometimes on a cycle ergometer). The nuclear stress test adds a radioactive tracer inserted intravenously to the patient to monitor blood flow through the heart. They are both used to evaluate heart disease in the form of coronary artery disease.

The current gold standard method for assessing aerobic exercise capacity in humans is the maximum incremental Cardiopulmonary Exercise Test (CPET). The CPET allows for measurement and analysis of ventilatory gas exchange during any of the above mentioned ergometry modes and protocols.

1.1.4. Evaluation of physical condition in diseased populations

Exercise testing is a very important tool in the diagnosis, evaluation, and prognosis of physical condition in diseased populations. Exercise testing is used in the diagnosis, evaluation, and prognosis of heart and pulmonary disease, as well as metabolic disease.

Aerobic capacity measured during exercise testing is also used in pre surgical assessment of different surgeries such as in gastric bypass surgery (surgical procedure where part of the stomach and small intestine is bypassed with the goal of losing weight by decreasing the size of stomach) (McCullough et al., 2006) and intraabdominal surgery (surgical procedure within the abdominal region) (Older, Hall, & Hader, 1999; Pescatello & American College of Sports, 2014).

Six-minute walk distance (6MWD) from a 6MWT is used to evaluate patients with lung or heart disease, in addition to other health limiting and debilitating conditions, (Alameri et al., 2007; Hassan, van der Net, Helder, Prakken, & Takken, 2008; Morinder, Mattsson, Sollander, Marcus, & Larsson, 2009; Ruden et al., 2011).

Exercise testing response is also used to evaluate severity of disease in chronic conditions such as Congestive Heart Failure (weakness of the heart muscle that fails to provide adequate blood flow to other tissues and organs), Pulmonary hypertension (PH) (disease characterized by high pulmonary blood pressures that if left untreated can lead to right heart failure and death), and chronic obstructive pulmonary disease (COPD) (chronic obstruction of lung airflow that interferes with normal breathing) (R. Arena, Myers, & Guazzi, 2010).

1.1.4.1. Clinical Exercise Testing in Heart Disease

Clinical exercise testing has been traditionally used as part of a differential diagnosis of coronary artery disease (CAD), although it is also indicated to assess functional capacity or prognosis.

Graded exercise testing, as in a treadmill Electrocardiogram (ECG) study (with or without echocardiography), is used as a diagnostic test for cardiovascular disease. In patients with

cardiovascular disease electrical changes in ECG, such as ST depression, represent ischemia or inadequate blood supply to the heart muscle (myocardium) at the coronary artery level. These changes at the coronary level are first seen with exertion. The importance of this diagnostic test is that it can be seen before other more sudden and dangerous changes happen, such as heart attack in the form of myocardial infarction (MI). It has the greatest posttest probability in patients with intermediate pretest probability of significant cardiovascular disease (CVD) (Mark et al., 1991). In other words in someone with intermediate risk factors (such as obesity, high cholesterol, high blood pressure, smoking history, sedentary life style, etc.) it has great probability on showing CVD. The severity of this CVD is evaluated based on the response to exercise. Magnitude of ischemia is directly proportional to degree of ST segment, number of leads involved, duration of ST segment depression in recovery, and inversely proportional to ST slope, Rate pressure product (RPP) at which ST depression occurs, maximum Heart Rate (HR max), Systolic Blood Pressure (SBP) and Metabolic Equivalent of Task (MET) achieved ("ACSM's guidelines for exercise testing and prescription," 2014). Untreated exercise ischemia can lead to inadequate supply of blood flow, or lack of oxygenation of the myocardium which in turn may lead to infarction and irreversible localized death of the heart tissue, as well as other heart conditions.

Peak Oxygen Uptake ($\dot{V}O_{2\text{max}}$), measured via CPET, has been widely used to assess functional capacity and predict survival in diseased populations such as those with advanced symptomatic heart failure (Cahalin, Mathier, Semigran, Dec, & DiSalvo, 1996; Oudiz et al., 2006). Pulmonary vascular resistance was found to increase as $\dot{V}O_{2\text{max}}$ (measured by CPET) and Cardiac Output, or

volume of blood pumped by the heart per unit time (CO), decreased in patients with heart failure (Butler, Chomsky, & Wilson, 1999).

Exercise testing can be used to determine functional capacity. Aerobic capacity (as in max or $\dot{V}O_2$) has been shown to be a better predictor of mortality than risk factors such as hypertension, tobacco use, etc. Studies performed on a cycle ergometer show that for each increase of 1 milliliter per minute per kilogram (ml/min/kg) of $\dot{V}O_2$ in aerobic capacity there was a 9-10% reduction in cardiac mortality ("ACSM's guidelines for exercise testing and prescription," 2014).

1.1.4.2.Clinical Exercise Testing in Pulmonary Disease

Exercise testing is an important factor in the diagnostic, evaluation, and management of patients with pulmonary disease. Shortness of breath is a common symptom for patients with lung disease. Exercise testing is helpful tool in confirming the disease's pathophysiology (disordered physiological processes associated with the disease) and helping with treatment.

The type of exercise test used will depend on the question that is to be answered and the availability of equipment. The 6MWT is the most commonly used test. This test represents a submaximal and motivational alternative compared to the CPET, and has shown correlation with CPET in COPD patients (Ciftci, Sen, Akkoca Yildiz, & Saryal, 2014; Poersch et al., 2013). 6MWT has been used in the evaluation of functional capacity in patients with COPD, interstitial lung disease or diffuse parenchymal lung disease (disease that affects the interstitium or tissue and space around the air sacs in the lung), among other pulmonary diseases. Exercise testing is also used as a very important tool in the evaluation of patients undergoing lung transplantation.

Longer 6MWD correlates with shorter Intensive Care Unit (ICU) stays after pediatric lung transplantation (Yimlamai, Freiburger, Gould, Zhou, & Boyer, 2013).

Peak VO_2 , measured via CPET, has been widely used to assess functional capacity and predict survival in patients with lung dysfunction (Cahalin, et al., 1996; Oudiz, et al., 2006). Aerobic capacity is of valuable prognostic value as well in interstitial lung disease and pulmonary hypertension, COPD, and possible in pulmonary fibrosis (condition that causes lung scarring and stiffness that may lead to reduced oxygen supply) (Ross Arena & Sietsema, 2011). CPET shows reduced exercise capacity in the form of low VO_2 , ventilatory limitation and normal cardiovascular response in patients with COPD and in patients with interstitial lung disease (Ross Arena & Sietsema, 2011; Donner, Carone, Patessio, & Appendini, 1994; Priegnitz, Hagmeyer, Kietzmann, Richter, & Randerath, 2015). Pulmonary vascular disease shows reduction in exercise capacity, but no ventilatory limitation and an abnormal cardiovascular response (Ross Arena & Sietsema, 2011).

Presurgical assessment of aerobic capacity has also been recognized as an important indicator of poor outcome in lung cancer patients (Loewen et al., 2007),

Exercise testing can elicit pulmonary mechanics limitations in COPD, where expiratory flow reaches limitation as well as dynamic hyperinflation of lung volumes. An increase in physiological dead space can also be seen (Ross Arena & Sietsema, 2011).

Exercise testing can bring up symptoms with exertion in patients with restrictive lung disease. An impaired gas exchange due to a decrease in alveolar-capillary interface is also seen with exercise. In interstitial lung disease there is an increase in the alveolar-arterial oxygen gradient and there is also an increase or not decrease of physiological dead space (Medicine, et al., 2012).

Most patients with significant interstitial lung disease may develop pulmonary hypertension with

exercise. Exercise can show the limitations of patients with vascular lung disease, such as PH. The exercise limitation in these patients is mostly caused by cardiac dysfunction, by a limiting stroke volume (Medicine, et al., 2012). Thus exercise testing is of such importance on the diagnosis, treatment and prognosis of PH, as it affects both the cardiovascular and pulmonary systems.

1.2. Pulmonary Hypertension

1.2.1. What it is

PH is a chronic disease characterized by high pulmonary blood pressures that if left untreated can lead to right heart failure and death. Pulmonary artery pressures are measured via right heart catheterization (RHC) gold standard, (Saggar & Sitbon, 2012). High pulmonary pressures are defined by a greater than 25 mm Hg mean Pulmonary Arterial Pressures (mPAP) (Vahanian & Ferrari, 2010) at rest and greater than 30 mm Hg during exercise (David B. Badesch et al., 2009). The pulmonary arterial hypertension (PAH) adds that a pulmonary arterial wedge pressure (PAWP) must be smaller than 15 mm Hg (David B. Badesch, et al., 2009). Figure 1 shows the anatomy of PH.

mPAP is determined by Pulmonary Vascular Resistance (PVR) or the resistance of flow in the pulmonary vascular system), CO (CO=Stroke Volume x Heart Rate), Left Atrial Pressures (LAP or pressures in the left atrium of the heart) as defined in the following equation $mPAP = PVR \times CO + LAP$ (Gregory D. Lewis et al., 2013; Naeije et al., 2013).

Figure 1. Anatomy of Pulmonary Hypertension From (Zeller, Burke, & Glass, 2009)

PH involves a vasoconstriction of the vessels connected to the lungs decreasing pulmonary blood flow (decreasing oxygenation) which can lead to right heart failure. Decreased pulmonary flow may lead to decreased systemic blood flow which in turn may lead to chronic low oxygenation of tissues.

Symptoms of PH include shortness of breath at rest or with exercise, fatigue, chest pain, dizziness or fainting spells, swelling of the ankles, abdomen or legs, bluish lips and skin.

Symptoms progress and become more severe as the disease progresses. Patients with PH have decreased exercise tolerance.

1.2.2. Diagnosing Pulmonary Hypertension

Although there are other non-invasive ways of measuring indirect pulmonary pressures (such as Trans Thoracic Echocardiogram (TTE)) the current gold standard in measuring pulmonary pressures is a RHC. RHC is an invasive method of measuring pulmonary pressures directly at the pulmonary artery. This type of invasive procedure involves a certain risk. Non invasive methods to measure (or estimate) pulmonary pressures are not completely accurate. However, echocardiograph methods can assess right atrial and ventricular size, atrial and ventricular septal contours, function, and pulmonary artery size as well as Tricuspid regurgitation via Doppler. This is helpful but still not as accurate as invasive RHC (Litwin, 2010), shown in figure 2.

Right heart catheterization

Figure 2. Right Heart Catheterization (Galié, et al., 2009)

PCWP= Pulmonary Capillary Wedge Pressure

1.2.3. Background History

Unexplained pulmonary hypertension was first diagnosed as a disease of the pulmonary vascular system by Romberg in 1891. In 1901 Ayerza noted cyanosis associated with pulmonary arteriosclerosis which he described as “cardiacos negros” to be later renamed Ayerza’s syndrome (Gaine & Rubin, 1998; Mazzei & Mazzei, 2011). However the term of primary pulmonary hypertension, as used today, was not described and named until 1951 by Dresdale and colleagues (Dresdale, Schultz, & Michtom, 1951).

From 1891 until 1951 there were no real advances in treating the disease until right heart catheterization was introduced. It was not until the late 1960 and 70's with the epidemic of aminorex-induced PAH that brought interest to the medical community, prompting in 1973 the first World Health Organization (WHO) meeting to address PH. The first clinical drug treatment did not come around until intravenous epoprostenol was approved in 1995 which led to many clinical trials in the last decades.

1.2.4. Prognosis, Prevalence, and Incidence

Prognosis varies depending on the etiology of the disease. It is a disease with poor outcome with some patients surviving for months and others for decades. However, the advances in treatment and therapies have significantly improved the outcome (V. V. McLaughlin et al., 2004).

There have been a few attempts to create national registries in the US. The first US registry started in 1981 included 187 patients from 32 centers. This registry determined that the mean age was 36 ± 15 with a female to male ratio of 1.7:1 (Rich et al., 1987). In another attempt to continue a national (US) registry for patients with Idiopathic (of unknown origin) Pulmonary Arterial Hypertension (IPAH) 194 patients from 32 centers diagnosed between 1981 and 1985 were followed through 1988. The estimated median survival rate for these patients was determined at 2.8 years (Gilbert E. D'Alonzo et al., 1991).

After looking at different populations the prevalence of PH was established at 15-50 cases per million. The incidence varies from 1-8 cases per million. IPAH is 2 to 4 times more common in women than in men (A. J. Peacock, Murphy, McMurray, Caballero, & Stewart, 2007). The largest and latest registry, Registry to Evaluate Early And Long-term pulmonary arterial

hypertension disease management (REVEAL Registry), was started in 2006 with roughly 3,000 patients enrolled. It is estimated that 40 % of the cases of Pulmonary Hypertension are IPAH, while the rest of them are mostly secondary to another disease (D. B. Badesch et al., 2010; Frost et al., 2011).

1.2.5. Classifications

International classification of diseases WHO

PH was classified within the international classification of diseases ICD-9-CM as a disease of the circulatory system, disease of pulmonary circulation, chronic pulmonary heart disease: Primary pulmonary hypertension 416.0; secondary pulmonary hypertension 416.8 (*ICD-9-CM: International Classification of Diseases, 9th revision, clinical modification, fifth edition, color coded, 1998, 1997*). In October 2015 it transitioned into ICD-10 as a disease of the circulatory system and under pulmonary heart disease and diseases of pulmonary circulation: Primary pulmonary hypertension I27.0 secondary pulmonary hypertension I27.2 (*ICD-10, 2014*).

Although one of the early studies on PH established pulmonary thrombosis as the major cause (Fuster et al., 1984), traditionally pulmonary hypertension has been classified in two groups, depending on its origin: primary pulmonary hypertension (Idiopathic) and secondary pulmonary hypertension. Secondary pulmonary hypertension is caused by some other disease, agent, or factor.

In the pediatric population PH is associated with idiopathic origin or Congenital Heart Disease (CHD). It is rarely associated with connective tissue disease or thromboembolic disease (Ivy et al., 2013).

The latest and updated classification for PH was established at the 5th symposium of pulmonary hypertension held in Nice (France) in 2013 (Simonneau et al., 2013), and it is shown in table 2:

Table 2. Latest Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension 1.1 Idiopathic PAH 1.2 Heritable PAH 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown 1.3 Drug and toxin induced 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis 1". Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease 2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due 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 lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms 5.1 Hematologic disorders: chronic hemolytic anemia , myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.

BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin;

HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

From the same symposium also came out a classification for drug and toxin induced PAH (Simonneau, et al., 2013) as shown in table 3:

Table 3. Updated Classification for Drug- and Toxin-Induced PAH*

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Interferon α and β
SSRIs[†]	Amphetamine-like drugs
Likely	Unlikely
Amphetamines	Oral contraceptives
Tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

*Nice 2013.

[†]Selective serotonin reuptake inhibitor (SSRIs) have been demonstrated as a risk factor for the development of persistent pulmonary hypertension in the newborn (PPHN) in pregnant women exposed to SSRIs (especially after 20 weeks of gestation). PPHN does not strictly belong to Group 1 (pulmonary arterial hypertension [PAH]) but to a separated Group 1. Main modification to the previous Danapoint classification are in **bold**.

Patients with PH are also classified based on their functional status as per the WHO. Table 4 shows the functional status classification.

Table 4. World Health Organization Classification of Functional Status of Patients**With PH** (McGoon et al., 2004)**Class Description**

I. Patients with PH 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 PH 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 PH 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 PH 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.

1.2.6. Treatment

The treatment of the disease consists of drug therapy and exercise therapy. All of these are adjusted depending on severity and response. The most common drugs are Prostaglandins (acting as a powerful local vasodilator), endothelin receptor antagonists (by decreasing pulmonary vascular resistance), and phosphodiesterase type 5 inhibitors (by lowering pulmonary arterial pressure and pulmonary vascular resistance). Blood thinners (to avoid thrombosis in certain forms of the disease) (Olsson et al., 2013; Said, 2014) and calcium channel blockers (by decreasing pulmonary pressures) (Sitbon et al., 2005) are also used, as well as oxygen (to maintain oxygenation levels) and controlled exercise therapy (to improve functional capacity among other effects) (Galiè et al., 2004).

The goal of therapy is to improve WHO functional class from III, IV to I and II , as well as class II to I or maintain class II (Robyn J. Barst et al., 2009). The current therapy algorithm is shown in the following figure 3:

Figure 3. Current consensus evidence-based guidelines for the treatment of pulmonary arterial hypertension (R. J. Barst, 2008). AVT (Acute Vasoreactivity Testing).

To evaluate the effectiveness of treatment follow up appointments with different evaluation tests are important. Exercise testing in the form of 6MWT and CPET are part of this diagnostic, evaluation tests, playing an important role on the adjustments of drug therapy.

When drug therapy and other treatments don't work, lung transplantation and atrial septostomy (surgical procedure where a small hole is created in the atrial septum to release pressure on the pulmonary circulation) are the only options.

1.3. Applications of Exercise Testing in PH

Exercise testing is an important tool in the assessment and evaluation of physical condition in the general population, in diseased populations, as well as in the diagnosis and prognosis of PH population. The most common exercise tests used in PH are the CPET (with measurement of ventilatory gas analysis) and the 6MWT. These tests also allow for measurement of functional capacity in PH and healthy populations. Both CPET and 6MWT are used as main endpoints for clinical trial studies. Exercise right heart catheterization is also a test used in PH to diagnose patients who may have PH with exercise.

1.3.1. Cardio Pulmonary Exercise Test

CPET “is an examination that allows the investigator to simultaneously study responses of the cardiovascular and ventilatory systems to a known exercise stress” (K. Wasserman, Hansen, & Sue, 2005). Gas exchange measured on a CPET is a consequence of CO, pulmonary flow, and oxygen (O₂) extraction at the muscle level. All these three systems work together to provide the muscle cells with the necessary O₂ and energy, and cannot be isolated, especially when exercising, as shown in figure 4. Thus CPET is vital in the analysis of all these three systems for the diagnosis, evaluation, and prognosis of the PH population. CPET allows an evaluation of the patient’s ability to perform exercise and what system causes exercise impairment. It allows assessing the cardiovascular, pulmonary, and metabolic systems during exercise. VO₂, HR, SBP and Carbon dioxide production (VCO₂) (all measured via CPET) are valuable measurements to investigate the interactions of these three systems (K. e. a. Wasserman, 2012) .

Figure 4. Interaction of cardiovascular, pulmonary, and metabolic systems. From (K. e. a. Wasserman, 2012).

The maximum incremental CPET stands as the current gold standard method for assessing aerobic exercise response in humans by obtaining peak/maximum $\dot{V}O_2$. The primary determinant of $\dot{V}O_2$ max is the functional capacity of the heart. $\dot{V}O_2 \text{ max} = \text{CO} \times \text{Arteriovenous oxygen difference}$. In a CPET the pulmonary respiration represents cellular respiration and can be measured non-invasively. The non invasive nature of a CPET makes it an easy tool that can yield a high amount of valuable information at the clinical level as well as at the performance and training levels. Exercise is limited by fatigue, dyspnea and/or pain.

CPET has been used to evaluate and compare characteristics of PH associated with other diseases such as COPD (Holverda et al., 2008), scleroderma (Alkotob et al., 2006), pulmonary fibrosis (Glaser et al., 2009), or along with 6MWT in chronic left heart failure (Deboeck, Niset, Vachieri, Moraine, & Naeije, 2005). The correlation between exercise testing and pulmonary pressures has also been studied. As mPAP increased Partial Pressure of End Tidal Carbon Dioxide (PETCO_2) was shown to be reduced when compared to normal patients (Yasunobu,

Oudiz, Sun, Hansen, & Wasserman, 2005). Exercise induced rise in PAP resulted in impairment of Right Ventricle (RV) function and underfilling of Left Ventricle (LV) both resulting in impaired Stroke volume (Holwerda, et al., 2008). CPET was used to measure PAP in patients with PH and sleep apnea at rest and during exercise (Podszus et al., 1986).

The ventilatory and gas exchange parameters obtained on a CPET, besides 6MWD, are great predictors of survival in patients with primary PH (H. Groepenhoff et al., 2008). In fact exercise pVO_2 and peak SBP were found to be strong survival predictors in patients with primary PH (Wensel et al., 2002).

CPET has been proven superior to other noninvasive testing to identify patients at high risk for heart catheterization (Rhodes, Barst, Garofano, Thoele, & Gersony, 1991). Poor exercise capacity (as a percent predicted of VO_2 max) in patients with primary PH put them at risk for RHC. Exercise testing is a useful noninvasive test to assess and evaluate physiological changes in primary PH patients (Garofano & Barst, 1999). It allows seeing changes before symptoms arise (Garofano & Barst, 1999). CPET has also been found to detect exercise induced right to left shunting in patients with PH (Sun, Hansen, Oudiz, & Wasserman, 2002).

CPET proves to be a great noninvasive diagnostic test for PH because it can diagnose the disease before symptoms arise. In the early stages of PH, the disease can be detected only with symptoms during exercise and not at rest. CPET can be the sole diagnostic test to diagnose PH in these patients who are asymptomatic or with normal pressures at rest who can feel symptoms when exercising (Alkotob, et al., 2006; Schwaiblmair, Faul, von Scheidt, & Berghaus, 2012; K. e. a. Wasserman, 2012). Pulmonary blood flow may be adequate at rest for these patients but may be difficult to increase during exercise. For some of these patients with exercise induced PH

a pulmonary artery catheter can add valuable information of their pulmonary pressures during exercise (K. e. a. Wasserman, 2012).

1.3.2. Six Minute Walk Test

6MWT has been mentioned earlier and it is explained in more detail here. As previously pointed out the 6MWT is a test where the maximum distance covered in six minutes is measured. 6MWT is a submaximal test that measures exercise tolerance. It evaluates the global and integrated responses of all systems involved in exercise.

The origins of the 6MWT go as far back as the 1960's when Balke developed a test to evaluate functional capacity by measuring distance and time ("ATS statement: guidelines for the six-minute walk test," 2002). Cooper later developed a 12 minute field test to measure physical fitness on healthy individuals, specifically US air force officers (Cooper, 1968). Other two and six minute walk test were developed for patients with respiratory disease who found a 12 minute walk exhausting (Butland, Pang, Gross, Woodcock, & Geddes, 1982). After examining all the different walk test it was found that the 6MWT was more researched and established and it was easy to perform, better tolerated and a more accurate reflection and measurement of activities of daily living (ADLs) for patients with cardiac and respiratory disease (Solway, Brooks, Lacasse, & Thomas, 2001). 6MWT provides useful information on daily physical performance in the form of a safe, simple, standardized, and inexpensive test. The 6MWT offers a better estimation of ADLs than other walk tests (Solway, et al., 2001). Limitation on ADLs, best reflected through 6MWT, have a strong association with prediction of mortality (Simon et al., 2011). The American Thoracic Society (ATS) has endorsed and published guidelines for performing the 6MWT in clinical settings ("ATS statement: guidelines for the six-minute walk test," 2002).

Thus the 6MWT is the walk test used for research and clinical purposes (Solway, et al., 2001). The 6MWT is also a very simple exercise test, which does not require expensive equipment. It is a good tool to evaluate physical fitness when gas exchange is not available (Chuang, Lin, & Wasserman, 2001).

The 6MWT is an independent predictor of morbidity and mortality in adult patients with heart failure (Cahalin, et al., 1996), left ventricular dysfunction (Bittner et al., 1993), chronic respiratory disease (Ashutosh & Dunskey, 1987), cystic fibrosis and PH (Oudiz, et al., 2006). Additionally, the 6MWT is a significant predictor of survival in patients with PH

(Benza et al., 2010; Herman Groepenhoff et al., 2013; Miyamoto, Nagaya, & Satoh, 2000; Paciocco et al., 2001; Timofte, Tonelli, Akindipe, & Baz, 2010), and is used in clinical trials for IPAH medication use (Mathai, Puhon, Lam, & Wise, 2012). Many studies have shown correlation between 6MWD and mortality: Patients who walked less than 332 meters in a 6MWT had a significantly decreased survival rate (Miyamoto, et al., 2000). The 6MWT is also used in other non PH groups such as in obese children and adolescents (Calders et al., 2008).

The 6MWT has become a standard of practice on the follow up of patients with PH, as well as a standard test for PH drug clinical studies.

1.3.3. Clinical Trials and Exercise Testing

Clinical trials are research studies that test the effectiveness and safety of certain medical approaches in people. The trials focus on prevention, screening, diagnosis, or treatment of a disease. Clinical trials have a protocol that needs to be approved by an Institutional Review Board (IRB). The IRB oversees the safety, ethical practices, rights and welfare of patients, as well as its risks. For a clinical trial to be efficient and safe there needs to be important end points. Exercise testing is one of the main end points as well as one of the most important prognostic

indicators in PH. 6MWT is most commonly used as a primary end point to many clinical trials. CPET provides a more sensitive exercise assessment than 6MWT, and more specifically for less ill diagnosis. VO_2 peak measured via CPET is prognostic in patients with PH (V. V. McLaughlin et al., 2009).

The first successful randomized clinical trial for PH was the epoprostenol infusion trial (R. J. Barst et al., 1996) that tested sheep models to study the disease and develop a treatment for PH in patients. This was the only trial that was FDA (Food and Drug Administration) approved based on improved survival of patients. All other FDA approved trials for PH therapies are based on improvement of hemodynamics, exercise capacity/6MWT and quality of life. Thus exercise capacity whether in the form of 6MWT and CPET is an important tool used regularly in clinical trials for the treatment of PH.

The future of clinical trials calls for exploration of new combination therapies including exercise (Rich, 2011).

1.3.4. Exercise Right Heart Catheterization

CPET can also be the sole diagnostic test to diagnose pulmonary hypertension in patients who are asymptomatic at rest but who can feel symptoms when exercising (K. e. a. Wasserman, 2012). In these patients a pulmonary artery catheter during an exercise test can add valuable information of their pulmonary pressures as seen in exercise induced pulmonary hypertension (K. e. a. Wasserman, 2012). In exercise induced PH pulmonary pressures are high during exercise but normal at rest. High pulmonary pressures with exercise are defined as higher than 30 mmHg at a CO of less than 10L/min (Naeije, et al., 2013). In many of these cases, untreated

exercise induced PH may lead to resting PH. This is of great importance because once resting symptoms arise the condition worsens and the opportunity to be treated with pulmonary vasodilator or anti-inflammatory may be lost. In these exercise induced PH populations VO_2 from CPET has been found to be decreased compared to normal patients but increased compared to population with resting PH (Tolle, Waxman, Van Horn, Pappagianopoulos, & Systrom, 2008).

1.4. Exercise Training

In the later years controlled submaximal exercise training has been proven to be a great tool in improving PH patient's quality of life and functional capacity. In fact exercise may be as beneficial as pharmacological therapy (A. Peacock & Peacock, 2013).

Lung transplantation was believed to be the only way to lower pulmonary vascular resistance in patients with PH who are unresponsive to vasodilator therapy. However, studies have shown that controlled exercise training programs may lead to significant improvements in not only exercise parameters but quality of life and even pulmonary pressures.

A controlled exercise training program in patients with PH improved 6MWD, quality of life scores, WHO functional class, peak VO_2 , O_2 pulse, HR, and systolic pulmonary artery pressure at rest and at peak exercise measured via Doppler echocardiography (Grunig et al., 2012). Training and patient education programs showed improvements in cardiorespiratory fitness and a decrease in fatigue (Weinstein et al., 2013). An increase in 6MWD, cardiorespiratory fitness, and patient reported improvement in quality of life was demonstrated after exercise training (Chan et al., 2013). A program of as little as three weeks of pulmonary and exercise training seemed enough to show improvement in greater 6MWD and increased magnetic resonance (MR) flow

and MR perfusion measured by MRI (Magnetic Resonance Imaging) (Ley et al., 2013). Longer periods of training such as 15 weeks of respiratory and exercise training demonstrated improvement in not only 6MWD but also scores of quality of life, WHO functional class, peak VO_2 , VO_2 at the AT, and achieved workload (Mereles et al., 2006) also there was an improvement in oxygen pulse, HR and systolic pulmonary artery pressure at rest and maximal workload (Grunig, et al., 2012). Other lengthy studies (12 weeks) confirmed higher workloads at the AT and overall workloads as well as an increase in capillarization and oxidative enzyme activity in the quadriceps after training (de Man et al., 2009).

The future of PH treatment may involve more exercise training. More clinical trials on exercise training in patients with PH are being conducted: Lucia et al. are currently studying the effects of whole muscle training in VO_2 peak, muscle strength, echocardiographic variables and functional capacity in patients with pulmonary hypertension, in their clinical trial “Whole muscle exercise training in pulmonary hypertension”.

After defining the indicators and markers of the disease, the possibility of evaluating PH patients in a simpler and more inexpensive way is explored. This would facilitate the inclusion of PH patients in training programs that would ultimately improve quality of life for these patients.

2. HYPOTHESIS AND GOALS

2.1. General

The goal is to establish new avenues to diagnose, evaluate and follow up subjects with IPAH via exercise testing and training.

It was hypothesized that exercise and exercise testing could be used as very important tools in the diagnosis, prognosis and evaluation of subjects with IPAH.

A descriptive study of different age groups was performed to establish differences between age groups in populations with IPAH. At the same time a comparison between healthy population and IPAH population is important. This would put into perspective how severe the disease is and how compromised these subjects can be in terms of their physical fitness and health status. Testing these diseased subjects can be a difficult task, as their health status and physical fitness is compromised at many different levels and it affects them on a daily basis by limiting their activities of daily living (ADLs). To better understand this population's limitation in terms of their functional capacity and what they can accomplish and do on a daily basis a study was performed. Thus VO_2 and METs on IPAH and healthy individuals were evaluated.

As the disease progresses it becomes difficult for patients with IPAH to perform a maximum effort (as in a CPET). It is hypothesized that the testing on these patients could be simplified with a submaximal exercise test as a 6MWT to predict VO_2 with its consequent value and applications. Thus the 6MWT could become a substitute for the CPET or at least it could diminish the frequency that a maximal effort such a CPET would need to be performed. In the

same line predicting mPAP from CPET would allow IPAH subjects to avoid, or at least decrease, the frequency of an invasive test such as the RHC.

2.2. Study 1

Hypothesis

Different IPAH age groups have different 6MWT and CPET values. Their values also differ from healthy groups.

Objectives

The objectives are:

- describing and comparing 6MWT and CPET for different age groups of patients with IPAH;
- describing and comparing IPAH adults with a control adult population;
- comparing children with IPAH with healthy children from Spanish schools.

2.3. Study 2

Hypothesis

IPAH patients are close to maxing out while performing a 6MWT, which may be a reflection of limitations on their ADLs.

Objectives

- The objective of this study is to compare the values and percentages of VO_2 max, and METs used during a 6MWT by IPAH age groups and how they compare to an adult healthy group.
- A secondary objective is to compare these values to activities of daily living (ADL) for all groups.

2.4. Study 3

Hypothesis

Peak VO_2 can be predicted from 6MWT.

Objective

- The aim of the present study is to determine whether the 6MWT is a predictor of Peak VO_2 in patients with IPAH and whether the 6MWT can be a surrogate for a CPET.

2.5. Study 4

Hypothesis

Higher cardiovascular fitness status (as reflected by CPET peak VO_2), correlates with better health status (as reflected by low mPAP).

Objective

- The objective is to explore if there is an indirect relationship between VO_2 and mPAP.

3. METHODOLOGY

3.1. Study 1

The study was conducted in accordance with the amended Declaration of Helsinki. The Columbia University Medical Center IRB approved the study protocol (ID #AAA0599) and waived the need for IPAH patient consent due to the retrospective nature of the study. However informed consent was obtained from the adult control group.

3.1.1. Subjects

157 patients with IPAH were tested. Patients were diagnosed by RHC (gold standard) measurement of mPAP greater than 25 mmHg and pulmonary arterial wedge pressure smaller than 15 mmHg at rest (David B. Badesch, et al., 2009; Hoeper, 2009). 99 patients were females and 58 were males. Of those 157 subjects there was only complete collection of data for 111 subjects. Those 111 subjects were divided into age categories: 31 children (6-12 years old), 28 adolescent (13-18), and 52 adults (19-60).

The adult healthy individuals were recruited from different sources. Some of these patients were students of the human nutrition program at Columbia University. Some others were friends, medical students, fellows or staff from New York Presbyterian Hospital/Columbia University Medical Center. It is understood the limitation in the randomization of the adult control group. 20 healthy subjects were used as a control adult population to compare with IPAH adults. Half of the control subjects were females and half were males.

There were 206 school children (from Spanish schools) (111 boys and 95 girls) that were administered a 6MWT and were compared to IPAH children. These children were recruited from different elementary schools around Madrid, Spain. It is understood the limitation of comparing children from Spain (as a control group) against diseased American children. However we had access to test these subjects and that is why they were used in the study.

3.1.2. Study Design

3.1.2.1. Procedure

IPAH subjects were tested in the exercise laboratory as their routine visit to the Pulmonary Hypertension Center of New York Presbyterian/Columbia University Medical Center. The IPAH and adult control groups were all tested in the pediatric exercise laboratory of Morgan Stanley Children's hospital of New York Presbyterian/Columbia University Medical Center.

Calibration was performed before each test as recommended by Wasserman (K. e. a. Wasserman, 2012).

Each patient (IPAH subjects and control adult group) performed Pulmonary Function Tests (PFTs), CPET, and a 6MWT. Demographics (height, weight and date of birth) were gathered prior to the test. Informed consent was obtained (from the control adult group) prior to enrolling in the study. The Columbia University Medical Center IRB approved the study protocol (ID #AAA0599) and waived the need for IPAH patient consent due to the retrospective nature of the study.

PFTs are a group of tests that measure how well the lungs work. PFTs measuring Forced Vital Capacity (via Spirometry), Slow Vital Capacity, and Maximum Voluntary Ventilation, were performed on a Breeze Suite CPX Ultima Medgraphics (St. Paul, Minnesota).

3.1.2.2. Cardio Pulmonary Exercise Test

The CPET was performed on a Lode Corival V2 (Groningen, The Netherlands) cycle ergometer following a ramp protocol with increments of 5,10,15,20 or 25 Watts/ minute (depending on fitness level and/or previous test) until exhaustion (volitional fatigue). Three minutes of baseline data were collected followed by three minutes of unloaded warm up cycling. The ramp protocol was started after the 3 minute warm up. Once the patient reached his or her maximum values, a 3 minute cool down of unloaded cycling was performed as part of a 10 minute recovery period, until return to baseline levels, and/or until symptoms, if any, resolved ("ACSM's guidelines for exercise testing and prescription," 2006). The following data was collected during the cycle ergometer test: time, work in watts, real time 12 lead Electrocardiogram with heart rate via Welch Allyn CardioPerfect (Delft, The Netherlands Skaneateles Falls, NY), systolic and diastolic blood pressure by auscultation and Baumanometer V-Lok blood pressure cuff (W.A. BAUMCO, INC. COPIAGUE, NY), non-invasive blood oxygenation (O_2 levels using finger and ear probe SpO_2) via 3900P Datex-Ohmeda Pulse Oximeter (Helsinki, Finland Madison, Wisconsin), O_2 uptake (absolute and adjusted for body weight), and other gas exchange parameters through breath by breath analysis of expired air via Breeze Suite CPX Ultima Medgraphics (St. Paul, Minnesota), as per Wasserman (K. e. a. Wasserman, 2012) and ACSM guidelines (Pescatello & American College of Sports, 2014) . The other gas exchange parameters measured, besides O_2 uptake, are the following: VCO_2 output (L/min), Ventilation (VE in

L/min), Tidal Volume (V_t in L), Respiratory Rate (RR in br/min), Partial Pressure of End Tidal Carbon Dioxide ($PETCO_2$ in mmHg), Partial Pressure of End Tidal Oxygen ($PETO_2$ in mmHg), Ventilatory equivalent for carbon dioxide (VE/VCO_2), Ventilatory equivalent for oxygen (VE/VO_2), and Respiratory Exchange Ratio (RER).

3.1.2.3. Six Minute Walk Test

The un-encouraged 6MWT was performed in a 30 meter hallway where the subject was instructed to walk as much as possible in 6 minutes by walking back and forth in the cited 30 meter hallway at their own speed and pace following ATS standards ("ATS statement: guidelines for the six-minute walk test," 2002; A. M. Li et al., 2007). Pulse oximetry via finger probe 3900P Datex-Ohmeda Pulse Oximeter (Helsinki, Finland; Madison, Wisconsin), Borg's CR10 scale (table 5) (Borg, 1998) (by subject choosing level of dyspnea from the scale), and Heart Rate (HR) in bpm, were measured at baseline and post-walk, as well as six minute walk distance (6MWD) in meters, and walking speed in m/min. To avoid learning effect subjects were not new to the test.

Table 5. Borg Rating Perceived Exertion Scale

0	Nothing at all
0.5	Very, very weak (just noticeable)
1	Very weak
2	Weak (light)
3	Moderate
4	Somewhat strong
5	Strong (heavy)
6	-
7	Very Strong
8	-
9	-
10	Maximal

3.1.3. Spanish School Children

The Spanish school children group was tested during their physical education classes. Age, height and weight were gathered prior to the test. Their test consisted of solely a 6MWT. The 6MWT was performed at a school gym. The course was the same as the one used at the Pulmonary Hypertension Center, 30 meter length flat straight surface, as recommended by ATS. Distance was tracked by classmates. HR was measured by counting heart rate in 6 seconds and then multiplying by 10. The equipment used in this group was the following: Stopwatch to measure 6 seconds to calculate HR and to time 6 minutes; Paper and pen to annotate number of laps.

3.1.4. Statistical Analysis

The data was statistically analyzed using the PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Data was checked for normal distribution and variables for each group were reported as mean $\pm$ Standard Deviation ($\pm$ SD). Two sample independent t tests with assuming either equal or unequal variances were performed to compare values between multiple groups. Significance was stated at $p < 0.05$. The validity of this p value depends on the following hypothesis being true: normal distribution, with equal or unequal variances, and the samples are representative of those populations. To decide whether to assume equal or unequal variances Levene's test was performed at a significance level of 0.05.

3.2. Study 2

The study was conducted in accordance with the amended Declaration of Helsinki. The Columbia University Medical Center Institutional Review Board approved the study protocol (ID #AAA0599) and waived the need for IPAH patient consent due to the retrospective nature of the study. However informed consent was obtained from the adult control group.

3.2.1. Subjects

111 number of patients with primary pulmonary hypertension were tested. Patients were diagnosed by right heart catheterization (gold standard) measurement of arterial pulmonary pressures greater than 25 mmHg and pulmonary arterial wedge pressures smaller than 15 mm Hg (David B. Badesch, et al., 2009; Hoeper, 2009). Subjects were stratified post-hoc by age into 3 groups (children; 6-12 years, adolescents; 13-18 years and adults; ≥ 19 years) for between-group comparison of anthropometric and 6MWT variables. There were 31 children (6-12 years old), 28 adolescent (13-18), and 52 adults (19-60). The participants are the same as study 1.

The adult control group was the same as study 1. It was recruited from different sources: students of the human nutrition program at Columbia University, acquaintances, medical students, fellows or staff from New York Presbyterian Hospital/Columbia University Medical Center. The limitation in the randomization of the adult control group is understood. The control group to be compared to the adult IPAH group consisted of 20 healthy subjects of whom half of them were male subjects and half of them female subjects.

3.2.2. Study Design

3.2.2.1.Procedure

IPAH children, adolescents, adults and adult control performed both a 6MWT and a CPET.

3.2.2.2.Cardiopulmonary Exercise Test

The CPET was performed following the same protocol as study 1.

3.2.2.3.Six Minute Walk Test

The un-encouraged 6MWT was performed in the same manner as study 1 following ATS standards ("ATS statement: guidelines for the six-minute walk test," 2002; Albert M. Li, Yin, Au, So, & et al., 2007; A. M. Li, et al., 2007).

3.2.3. Statistical Analysis

The data was statistically analyzed using the PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Data was presented as mean $\pm$ standard deviation (Mean $\pm$ SD). An analysis of variance (ANOVA) was employed to determine differences between anthropometric and 6MWT variables between the three age groups.

Mean peak VO_2 from CPET was calculated for each group as well as mean estimated VO_2 during 6MWT by using the ACSM formula ("ACSM's guidelines for exercise testing and prescription," 2006). $\text{VO}_2 = 0.1 \times \text{Speed}(\text{m/min}) + (1.8 \times \text{Speed} \times \text{Grade}) + 3.5$. Mean peak VO_2 and mean estimated VO_2 during 6MWT were compared to establish percentage of peak VO_2 used during the 6MWT by all different groups.

3.3. Study 3

The study was conducted in accordance with the amended Declaration of Helsinki. The Columbia University Medical Center Institutional Review Board approved the study protocol (ID #AAA0599) and waived the need for patient consent due to the retrospective nature of the study.

3.3.1. Subjects

157 patients being treated for IPAH from 2003 to 2013 were included in this study. Patients were diagnosed with IPAH by right heart catheterization measurement of arterial pulmonary pressures greater than 25 mmHg and pulmonary arterial wedge pressures smaller than 15 mm Hg (David B. Badesch, et al., 2009; Hoeper, 2009). Subjects were stratified post-hoc by age into 3 groups (children; 6-12 years, adolescents; 13-18 years and adults; ≥ 19 years) for between-group comparison of anthropometric and 6MWT variables. Among the 26 children, mean age was 9.96 ± 1.66 and 73% were female. Among the 49 adolescents, mean age was 15.33 ± 1.80 and 47% were female. Among the 82 adults, mean age was 27.33 ± 6.70 and 69.5% were female.

3.3.2. Study Design

3.3.2.1. Procedures

The subjects were tested in the pediatric exercise laboratory as a standard of care for IPAH visit to the Pulmonary Hypertension Center of New York Presbyterian/Columbia University Medical Center. Each patient performed Pulmonary Function Test, CPET, and a 6MWT all within the same day. Height, weight and age were gathered prior to the test. Patients were not new to the test.

3.3.2.2. Pulmonary Function Test

Forced Vital Capacity (via Spirometry), Slow Vital Capacity, and Maximum Voluntary Ventilation were measured. Pulmonary function tests were performed on a Breeze Suite CPX Ultima Medgraphics (St. Paul, Minnesota).

3.3.2.3. Cardiopulmonary Exercise Test

CPET was performed following same protocol as study 1 and 2.

3.3.2.4. Six Minute Walk Test

6MWT was performed following the same protocol as study 1 and 2.

3.3.3. Statistical Analysis

The data were statistically analyzed using the PASW Statistics, version 18.0, for Windows (SPSS Inc, Chicago, IL). Continuous variables were presented as mean $\pm$ standard deviation. To evaluate whether anthropometric and 6MWT variables were different between the 3 groups, analysis of variance (ANOVA) was used. Three multiple linear regression models, one for each group of participants, were determined. Variables such as weight, height, BMI, sex, walk speed, resting heart rate, and RPE were included in the analyses. A backward elimination approach was used to finalize the regression models. If the slope for an independent variable was not found to be statistically significantly different than zero at $\alpha = .05$, that independent variable was excluded from the model. To assess the fit of the predictive model, we used conventional linear regression models according to the coefficient of determination (R^2). A paired Student t test was used to compare the mean values for the measured and the estimated peak VO_2 measurements. Pearson

correlation coefficient (r) was used to assess the linear bivariate relationship among estimated and measured peak VO_2 . For all tests, a P value $< .05$ was considered statistically significant.

3.4. Study 4

3.4.1. Subjects

157 number of patients with primary pulmonary hypertension were tested. Patients were diagnosed by right heart catheterization (gold standard) measurement of mean arterial pulmonary pressures greater than 25 mmHg and pulmonary arterial wedge pressures smaller than 15 mm Hg (David B. Badesch, et al., 2009; Hoeper, 2009). Of all the 157 patients there were only 17 who underwent both a CPET and a pulmonary artery catheterization within an established maximum of 10 days of each other, to avoid significant changes that would affect mPAP, at least a total of 3 times. It was established that in a stable patient within ten days there would not be major changes that would affect mPAP or CPET values. Therefore 10 days was established as a reasonable amount of time between CPET and right heart catheterization although other studies involving CPET and RHC established one month as a reasonable time between the two tests (Sun, Hansen, Oudiz, & Wasserman, 2001). Each of these patients had these two procedures performed (within ten days of each other) at least three times over a period of a few years. Thus correlation between mPAP and pVO_2 could be explored. There were 7 males and 10 females. The characteristics of the total of 59 visits over time of these 17 subjects are shown in table 6.

Table 6. Characteristics of the 59 visits.

Resting data				Peak data		
Age	16	±	8	16	±	8
Height						
(cm)	154	±	19	154	±	19
Weight						
(kg)	48	±	20	48	±	20
mPAP at rest						
(mmHg)	46	±	22	46	±	22
VO ₂						
(ml/min)	244	±	113	1349	±	781
VO ₂						
(ml/kg/min)	5	±	2	25	±	11
VCO ₂						
(ml/min)	214	±	100	1492	±	909
VE (l/min)	10	±	3	53	±	23
VE/VO ₂	47	±	21	42	±	14
VE/VCO ₂	52	±	24	38	±	12
HR (bpm)	91	±	14	165	±	23

O ₂ Pulse						
(ml/beat)	3	±	1	8	±	4
SBP						
(mmHg)	107	±	13	142	±	24
DBP						
(mmHg)	74	±	9	73	±	7
PETO ₂						
(mmHg)	112	±	6	118	±	8
PETCO ₂						
(mmHg)	34	±	5	34	±	7

3.4.2. Study design

3.4.2.1.Procedure

Subjects underwent CPET as part of their routine follow up visit within the Pulmonary Hypertension Center of Columbia University Medical Center. As part of their visit they also underwent a Right Heart Catheterization to measure pulmonary pressures at the pulmonary artery. Only the subjects who underwent both CPET and right heart catheterization within ten days of each other, a combined of at least three times, were included in the retrospective analysis.

3.4.2.2.Cardiopulmonary Exercise Test

CPET followed same protocol as study 1, 2, and 3.

3.4.2.3.Right Heart Catheterization

Prograde Catheterization technique was performed both via femoral or internal jugular venous access, and in some cases via femoral arterial access. Catheters were run into the right atrium and eventually into the pulmonary artery where right atrial, pulmonary artery, and pulmonary capillary wedge pressures were measured (Zuckerman et al., 2013).

3.4.3. Statistical Analysis

The data was statistically analyzed using the PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Data was presented as mean $\pm$ standard deviation (Mean $\pm$ SD).

Correlation between mPAP and pVO₂ measurements is explored for all 17 subjects. However, this correlation does not allow exploring correlation for various measurements within the same individual. As it was not viable to get 20 measurements for each individual 3-5 measurements for each subject were collected, with a total of 59 paired measurements of mPAP and pVO₂. This could be analyzed with more sophisticated statistical measurements for repeated measurements, as in generalized linear models. Since that was not viable a more simple descriptive statistical analysis of these 17 individuals with just a simple random measurement of paired variables was explored. The characteristics of the 17 subjects are shown in table 7.

Table 7. Characteristics of the 17 patients.

	Resting data			Peak data		
Age	17.64	±	8.56	17.65	±	8.56
Height						
(cm)	159.00	±	17.27	159.00	±	17.27
Weight						
(kg)	52.05	±	19.91	52.05	±	19.91
mPAP at rest						
(mmHg)	45.18	±	19.05	45.18	±	19.05
VO ₂						
(ml/min)	224.94	±	84.58	1386.24	±	700.29
VO ₂						
(ml/kg/min)	4.71	±	1.63	27.64	±	10.84
VCO ₂						
(ml/min)	206.94	±	83.27	1601.06	±	916.82
VE (l/min)	9.74	±	2.96	54.02	±	25.98
VE/VO ₂	48.00	±	19.06	40.18	±	7.51
VE/VCO ₂	50.76	±	19.79	35.94	±	8.30
HR (bpm)	91.82	±	13.43	165.59	±	27.07

O ₂ Pulse						
(ml/beat)	2.59	±	1.12	8.12	±	2.96
SBP						
(mmHg)	104.59	±	11.51	143.71	±	27.42
DBP						
(mmHg)	75.29	±	7.39	72.94	±	6.14
PETO ₂						
(mmHg)	113.59	±	5.15	117.88	±	6.32
PETCO ₂						
(mmHg)	33.44	±	4.08	34.97	±	4.81

4. RESULTS

4.1. Study 1

4.1.1. Describing and Comparing IPAH Groups

Since samples were approximately symmetrical the Means and SD calculated are representative summaries of the sample. The characteristics of the participants are shown on table 8.

Table 8. Characteristics of the IPAH population.

	Children (n=31)		Adolescents (n=28)		Adults (n=52)	
Age	9.68	± 1.96	15.11	± 1.45*	31.17	± 9.66*#
Height (cm)	136.90	± 13.29	163.36	± 7.94*	165.64	± 8.33*
Weight (kg)	31.89	± 10.66	57.92	± 17.34*	70.41	± 19.44*#
BMI (kg/m ²)	16.63	± 2.93	21.65	± 6.22*	25.53	± 6.02*#
Mean PAP at rest (mmHg)	44.65	± 18.40	46.96	± 24.30	50.42	± 17.95
Peak VO ₂ (ml/min)	711.68	± 189.23	895.36	± 425.52*	982.88	± 452.36*
6MWD (m)	423.10	± 87.83	452.36	± 88.59	443.94	± 82.41
Walk Speed (m/min)	70.52	± 14.64	75.39	± 14.76	73.99	± 13.73
Dyspnea Borg (0-10)	1.18	± 1.34	0.89	± 1.12	1.19	± 1.78
Peak VO ₂ (ml/kg/min)	16.08	± 5.09	19.91	± 8.01*	19.64	± 6.59*

Note. BMI: body mass index; HR: heart rate; 6MWD: six minute walk distance; Peak VO₂: peak oxygen consumption per body mass.

*Significantly different from children (p<0.05); #Significantly different from adolescents (p<0.05).

Independent t-test revealed significant differences between children and adolescents with IPAH in demographics (height, weight, BMI, age), peak VO_2 absolute, and peak VO_2 adjusted by body weight. However, no significant differences were found in mean PAP at rest, distance, walk speed, and dyspnea.

Comparison between children and adults with IPAH revealed differences in height, age, absolute peak VO_2 and adjusted peak VO_2 , and BMI. However no significant differences were found in mean PAP, distance, walk speed and dyspnea.

Comparison between adolescents and adults with IPAH demonstrated significant differences in age, weight, and BMI. No significant differences were found in height, mean PAP at rest, pVO_2 absolute and pVO_2 adjusted for body weight, distance, walk speed, and dyspnea.

4.1.2. Describing and Comparing IPAH Adults and Healthy Adults

The characteristics of the 52 adults with IPAH and 20 healthy adults are shown in the following table 9:

Table 9. Comparative of IPAH adults and Adults control.

	IPAH Adults (n=52)			Adults Control (n=20)		
Age	31.17	±	9.66	29.05	±	5.66*
Height						
(cm)	165.64	±	8.33	167.6	±	10.19
Weight						
(kg)	70.41	±	19.44	66.73	±	15.06
BMI						
(kg/m ²)	25.53	±	6.02	23.51	±	3.58
6MWD (m)	443.94	±	82.41	632.85	±	105.55*
Walk						
Speed						
(m/min)	73.99	±	13.73	105.47	±	17.59*
Peak VO ₂						
(ml/kg/min)	19.64	±	6.59	36.91	±	13.25*
Dyspnea						
Borg (0-10)	1.19	±	1.78	1.02	±	1.09

Note. BMI: body mass index; HR: heart rate; 6MWD: six minute walk distance; Peak VO₂: peak oxygen consumption per body mass.

*Significantly different from IPAH adults (p<0.05);

The comparison between the adult IPAH group and the healthy adult group revealed significant differences in age, 6MWD, walk speed, and pVO_2 .

The t-test demonstrated no significant differences in height, weight, BMI, and dyspnea score.

4.1.3. Describing and Comparing IPAH Children and Healthy Children

Both children groups (IPAH and Spanish school children) have similar distributions and are very homogeneous as shown in table 10.

Table 10. Comparison of IPAH children and Healthy children.

IPAH Children (n=31)			Healthy Children (n=206)		
Age	9.68	± 1.96	9.63	± 1.21	
Height					
(cm)	136.9	± 13.29	140.99	± 9.12	
Weight					
(kg)	31.89	± 10.66	37.14	± 9.03*	
BMI					
(kg/m ²)	16.63	± 2.93	18.46	± 2.93*	
6MWD					
(m)	423.1	± 87.83	752.94	± 66.04*	
Walk					
Speed					
(m/min)	70.52	± 14.64	125.49	± 11.01*	

Note. BMI: body mass index; HR: heart rate; 6MWD: six minute walk distance; Peak VO₂: peak oxygen consumption per body mass.

*Significantly different from children (p<0.05);

Significant differences between healthy Spanish school children and US children with IPAH were found in weight, distance, speed and BMI.

There were no significant differences in age and height.

4.2. Study 2

4.2.1. Comparing 6MWT and CPET in IPAH and Healthy Populations

Baseline characteristics of the sample are shown in **tables 8 and 9 (same as study 1)**.

Children (31) with IPAH averaged an estimated 10.6 ml/kg/min VO_2 (estimated 3 METs) during their 6MWT. Children with IPAH are estimated to be working at a 69% of their peak VO_2 (15.4 ml/kg/min or 4.4 METs) during their 6MWT. Figure 5 shows the comparison between pVO_2 from CPET and from 6MWT in IPAH children.

Figure 5. Comparison between pVO_2 obtained from CPET and pVO_2 calculated for 6MWT in the IPAH children population.

Adolescents (28) with IPAH used a calculated average of 11 ml/kg/min VO_2 (estimated 3.1 METs) during their 6MWT while this accounts for 63.5% of their measured peak VO_2 (17.3 ml/kg/min or 5METs) on the bike test (see figure 6).

Figure 6. Comparison between pVO₂ obtained from CPET and pVO₂ calculated for 6MWT in the IPAH adolescent population.

Adult IPAH patients (n=52) averaged an estimated 10.9ml/kg/min (3.1 estimated METS) during the 6MWT, compared to the 19.6 ml/kg/min peak VO_2 from the CPET as shown in figure 7.

Figure 7. Comparison between pVO₂ obtained from CPET and pVO₂ calculated for 6MWT in the IPAH adult population.

The adult healthy control group (n=20) averaged 14ml/kg/min VO₂ (estimated 4 METs) during the 6MWT. However, when comparing the estimated VO₂ during the walk with peak VO₂ from the bike test, the healthy group only uses a calculated 43% of their measured (32.6 ml/kg/min or 9.3 METs) bike peak VO₂ (see figure 8), while the adult IPAH group uses a calculated 55.6% of 19.6 ml/kg/min peak VO₂ (5.6 METs).

Figure 8. Comparison between pVO₂ obtained from CPET and pVO₂ calculated for 6MWT in the adult control population

IPAH children used 69% of their pVO₂ during the 6MWT while IPAH adolescents used 63.5%, IPAH adults 55.6%, and healthy adults 43% as shown in figure 9.

Figure 9. Comparison of the percent pVO₂ used during the 6MWT by all groups.

Figure 10 and 11 show a comparison of VO_2 values for all groups used both during 6MWT and CPET.

Figure 10. Comparison between pVO_2 obtained from CPET and pVO_2 calculated for 6MWT for all groups.

Figure 11. Comparison between average pVO₂ obtained from CPET and average pVO₂ calculated for 6MWT for all groups.

The total IPAH population (including the children, adolescent, and adult groups) averaged a calculated VO₂ during the 6MWT of 10.8 ml/kg/min or 3.1 estimated METs. This averages a 64% of measured peak VO₂ (average 16.9 ml/kg/min).

4.2.2. Comparing Activities of Daily Living for all Groups

Figure 12 shows a comparison of average METs obtained from 6MWT and CPET for all IPAH and healthy adult groups.

Figure 12. Comparison between average METs obtained from CPET and average METs calculated for 6MWT for all groups.

In an effort to compare functionality of IPAH and healthy subjects to the general population a compendium of physical activities with MET values (Ainsworth et al., 2011) was plotted.

Comparison of activities by METs

Figure 13. Comparison of activities of daily living by MET values including all study groups (see full compendium of ADLs in Appendix section)

Adult subjects with IPAH walked at 3.1 METs while their peak maximal effort reached 4.8 METs. Activities of daily living or ADLs are generally measured in METs or Metabolic Equivalent of Task. A resting metabolic rate of 3.5 ml/kg/min is equal to 1 MET. In a normal population the norm is to have at least a 7 fold increase of MET levels during peak exercise (Fletcher et al., 1995). In subjects with IPAH this increase is reduced to a 4 fold increase (Butler, et al., 1999; G. E. D'Alonzo et al., 1987). The healthy adult group had an average 9 fold increase while adult IPAH patients had a 3 fold increase. Thus IPAH subjects have significant functional capacity limitations.

When comparing these MET levels to ADLs, adult patients with IPAH, while working at 55.6% of their max or 3.1 METs, would not be able to sustain for long periods of time any of the following activities: walking at a moderate pace 2.8-3.2 mph, cleaning or sweeping, raking leaves, gardening, pushing a stroller or walking with children, etc. As these patients reach their max levels (4.8 METs) some of the following activities would be completely out of their reach. They would not be able to do them for even a few seconds (dancing ballet, moving lifting light loads, painting, digging, shoveling, mowing the lawn, carrying 15 pound loads up or down the stairs, etc.).

Children with IPAH walking at 69% of their peak VO_2 averaging 3 METs would not be able to sustain any of these activities for more than 6 minutes without stopping: bicycling at a leisurely pace, marching band, playing trombone while standing, swimming, canoeing, rowing, gymnastics, horseback riding, softball, etc. With a peak MET value of 4.4 these children would

not be able to do any of the following activities even for a few seconds: basketball, tennis, soccer, unicycling, moderate skateboarding, kayaking, using crutches, skiing, hopscotch, dodge ball, etc.

Adolescents with IPAH at 3.1 METs level of activity would not be able to sustain any of the following activities for much more than 6 minutes: marching band, bicycling at a moderate pace, basketball, tennis, etc. With a peak MET level of 5 these patients would not be able to do any of the following activities for even a few seconds: martial arts, hiking at a normal pace, badminton, ice skating, canoeing, swimming laps, basketball, etc.

4.3. Study 3

The baseline characteristics of the sample are shown in **Table 11**.

Table 11. Characteristics of the IPAH participants and 6MWT data.

	Children (n=26)		Adolescents (n=49)		Adults (n=82)	
Age	9,96	± 1,66	15,33	± 1,80	27,33	± 6,70
Height (cm)	140,15	± 12,88	160,98	± 9,48*	164,67	± 8,24*#
Weight (kg)	35,09	± 13,31	52,42	± 17,80*	62,85	± 19,16*#
BMI (kg/m ²)	17,37	± 3,81	19,98	± 5,47	23,02	± 5,96*#
Resting HR (bpm)	90,19	± 22,01	88,31	± 15,95	83,84	± 15,51
Peak HR (bpm)	153,12	± 26,22	152,04	± 20,88	137,10	± 28,58*#
6MWD (m)	471,15	± 89,43	455,78	± 84,63	459,77	± 115,12

Walk Speed (m/s)	1,31	± 0,25	1,27	± 0,24	1,28	± 0,32
Dyspnea Borg (0-10)	1,60	± 2,11	0,99	± 1,30	1,31	± 1,44
Peak VO_2 (ml/kg/min)	22,07	± 6,67	20,59	± 6,23	16,03	± 6,33

Note. BMI: body mass index; HR: heart rate; 6MWD: six minute walk distance; Peak VO_2 : peak oxygen consumption per body mass.

*Significantly different from children ($p < 0.05$); #Significantly different from adolescents ($p < 0.05$).

ANOVA revealed significant differences between age groups for height ($F_{2,156}=66.384; p < 0.001$), weight ($F_{2,156}=24.453; p < 0.001$), BMI ($F_{2,156}=11.943; p < 0.001$), and peak heart rate ($F_{2,156}=6.8; p = 0.001$). No significant differences were found between groups for resting heart rate ($F_{2,156}=1.91; p = 0.152$), walk distance ($F_{2,156}=0.195; p = 0.823$), walk speed ($F_{2,156}=0.195; p = 0.823$) and Rate of Perceived Exertion (RPE) ($F_{2,156}=1.39; p = 0.252$).

Among the 26 children, mean age was 9.96 ± 1.66 years and 73% were female. In the group of adolescents ($n = 49$), mean age was 15.33 ± 1.86 years and 47% were female. Among the 82 adults, mean age was 27.33 ± 6.70 years and 69.5% were female.

For the linear regression analysis, 3 independent multiple linear regressions were modeled after the three groups (children, adolescents, adults). The variables—sex (0 = female, 1 = male); weight; height; BMI; walk speed; resting heart rate; and RPE—were included in the models. Final models included variables that yielded the highest R^2 values.

Table 12 shows the standardized and nonstandardized coefficients for the linear regression model. Using standardized coefficients, in the first model (children), weight, BMI, and height (-4.72 , 3.10 , and 1.44 , respectively) contributed most to the model that predicted peak VO_2 . The remaining variables (sex, walk speed, RPE, and resting heart rate) contributed less to the prediction. In the second model (adolescents), the walk speed contributed most to the prediction model while RPE and height contributed less. In the third model (adults), the variable that contributed the most was 6MWD (0.48), before sex (0.30), height and weight to estimate peak VO_2 .

Table 12. Standardized and no-standardized coefficients of the linear regression models for VO₂ peak prediction.

	Children (R ² =0.834)			Adolescents (R ² =0.322)			Adults (R ² =0.479)		
	Standardize d	Un- standardize d	p-value	Standardize d	Un- standardized	p- value	Standardize d	Un- standardize d	p-value
Constant		-108.975			32.427			-21.626	
Sex	0.342	5.043	0.002	-	-	-	0.301	4.103	0.002
Height	1.436	0.759	0.024	-0.245	-0.167	0.05	0.224	0.174	0.043
Weight	-4.720	-2.366	0.002	-	-	-	-0.217	-0.071	0.020
BMI	3.101	5.429	0.003	-	-	-	-	-	-
Walk Speed	0.770	20.667	<0.001	0.497	13.326	<0.001	-	-	-
6MWD	-	-	-	-	-	-	0.480	0.026	<0.001
Rate of Perceived Exertion	-0.562	-1.78	<0.001	-0.359	1.737	0.006	-	-	-
Resting Heart Rate	-0.290	-0.136	0.006	-	-	-	-	-	-

The first model (Children) obtained a coefficient of determination (R²) of 0.834. The model equation was:

$$\text{Peak VO}_2 (\text{children}) = -108.975 + (5.043 \times \text{Sex}) + (0.759 \times \text{Height}) - (2.366 \times \text{Weight}) + (5.429 \times \text{BMI}) + (20.667 \times \text{Walk Speed}) - (1.780 \times \text{Rate of Perceived Exertion}) - (0.136 \times \text{Resting Heart Rate})$$

The second model (Adolescents) created obtained a coefficient of determination (R²) of 0.322.

The model equation was:

$$\text{Peak VO}_2 (\text{adolescents}) = 32.427 - (0.167 \times \text{Height}) + (13.326 \times \text{Walk Speed}) - (1.737 \times \text{Rate of Perceived Exertion})$$

The third model (Adults) obtained a coefficient of determination (R^2) of 0.479. The model equation was:

$$\text{Peak } VO_2 (\text{adults}) = -21.626 + (4.103 \times \text{Sex}) + (0.174 \times \text{Height}) - (0.071 \times \text{Weight}) + (0.026 \times \text{6MWD})$$

Assessment by the Student t test showed no significant differences between the measured and the estimated peak VO_2 for children, adolescents, and adults. There were significant correlations between measured and estimated peak VO_2 for the 3 groups (children, $r^2 = 0.873$; adolescents, $r^2 = 0.591$; and adults, $r^2 = 0.681$, $P < .001$ for all). Figure 14 shows this correlation between measured peak VO_2 from the exercise test (peak VO_2 -CPET) and estimated peak VO_2 from 6MWT (peak VO_2 -6MWT) for all 3 groups (children, adolescents, and adults) expressed in mL/kg/min.

CHILDREN

ADOLESCENTS

ADULTS

Figure 14. Correlation between measured pVO_2 from CPET and estimated pVO_2 from 6MWT

4.4. Study 4

The objective is to explore if there is an indirect relationship between VO_2 and mPAP.

Correlation between mPAP and pVO_2 absolute for the 17 individual measurements was slightly positive at a 0.04. When pVO_2 is adjusted for body weight correlation between mPAP and pVO_2/kg shows a negative -0.11 value.

Figure 15. Correlation between mPAP and pVO_2 .

Figure 16. Correlation between mPAP and pVO₂ adjusted for body weight

Average of individual correlations for all 59 visits of mPAP vs pVO₂ is 0.32. Median of individual correlations of mPAP vs pVO₂ is 0.46. There were 6 negative correlations and 11 positive correlations between mPAP and pVO₂. Correlations were compared to mean mPAP due to normal distribution of mPAP (see table 13).

Table 13. Correlations between mPAP and pVO₂ above and below the mean of mPAP.

Comparison with Mean of mPAP				
	Above	mean	Below	mean
	mPAP		mPAP	Total
<hr/>				
Correlation				
Positive	6		5	11
Negative	3		3	6
Total	9		8	17

Correlations between mPAP and pVO₂ were compared to median pVO₂ because of the abnormal distribution of pVO₂. Median pVO₂ is a better representation of the sample (see table 14).

Table 14. Correlations between mPAP and pVO₂ above and below the median of pVO₂.**Comparison with median pVO₂**

	Above pVO₂	median pVO₂	Below pVO₂	median pVO₂	Total
Correlation					
Positive	5		6		11
Negative	2		4		6
Total	7		10		17

Average of individual correlations of mPAP and adjusted pVO₂ is 0.00. Median of individual correlations of mPAP vs adjusted pVO₂ is 0.00. Correlations between mPAP and adjusted pVO₂ were compared to mean mPAP because of the normal distribution of mPAP. Above the mean mPAP correlations tend to be positive, below the mean mPAP correlations tend to be negative (see table 15).

Table 15. Correlations between mPAP and adjusted pVO₂ above and below the mean of mPAP.

Comparison with Mean of mPAP				
	Above	mean	Below	mean
	mPAP		mPAP	Total
Correlation				
Positive	6		3	9
Negative	3		5	8
Total	9		8	17

Correlations between mPAP and adjusted pVO₂ were compared to median pVO₂ because of the abnormal distribution of adjusted pVO₂ (see table 16). Median adjusted pVO₂ is a better representation of the sample.

Table 16. Correlations between mPAP and adjusted pVO₂ above and below the median of adjusted pVO₂.

Comparison with median adjusted pVO₂

	Above pVO ₂	median pVO ₂	Below pVO ₂	median Total
Correlation				
Positive	4		5	9
Negative	3		5	8
Total	7		10	17

The subject with most visits (5) showed significant positive correlation (0.94) between mPAP and absolute pVO₂, but no correlation between mPAP and adjusted pVO₂. Curiously that subject also showed significant positive correlation (0.77) between mPAP and pSBP.

Highest significant negative correlations between mPAP and pVO₂ (-0.99) as well as between mPAP and adjusted pVO₂ (-0.95) were shown in patients with just 3 visits over time.

Correlation between mPAP and pSBP was briefly explored with significant (0.36) positive relationship. Figure 17 shows that correlation.

Figure 17. Correlation between pSBP and mPAP

5. DISCUSSION

5.1. Study 1

Study 1 described and compared 6MWT and CPET for different age groups of individuals with IPAH and between IPAH populations and healthy populations. Emphasis was made on describing and comparing the children population of IPAH with healthy children, as there is limited literature focusing on these groups.

5.1.1. IPAH Groups

When comparing IPAH groups the following were found:

Mean PAP at rest between IPAH groups was found to be similar. The results showed that the distance walked by these patients does not vary much with age, height or weight as opposed to what previous studies have shown (Calders, et al., 2008; Casanova et al., 2011; Chetta et al., 2006a, 2006b; P. L. Enright & D. L. Sherrill, 1998a; Klepper & Muir, 2011). 6MWD is affected by height, weight, FEV1, BMI, and less importantly HR at the end of the test (Geiger et al., 2007; Klepper & Muir, 2011; Lammers, Hislop, Flynn, & Haworth, 2008; Albert M. Li, et al., 2007; Oliveira et al., 2013; Ulrich et al., 2013). However, there were no significant differences in 6MWD among IPAH groups regardless of significant differences in height (except between adolescent and adult IPAH groups), weight, BMI, and age.

The study may suggest that the main reason for achieving a certain distance during the six minute walk test is the patients' health status as reflected by mPAP or simply by their diagnosis. Even though dyspnea seems to be a rather subjective score, there are no significant differences in dyspnea scores between all three groups of IPAH. This goes in concordance with their health

status and their mPAP. Thus 6MWD did not appear to be affected by height, age, and weight in different groups of IPAH subjects rather than by diagnosis or mPAP.

These results suggest that mPAP at rest and 6MWD could have an important relationship that may need to be explored in this population. This relationship opens a future line of investigation. If such relationship were to exist correlation as well as prediction of mean PAP from 6MWD could be explored. If this relationship was to be true it could open up the possibility that 6MWD could eventually be used to predict mPAP, eventually avoiding the invasive (and with certain risk) procedure of right heart catheterization or at least decreasing the frequency with which that RHC is performed.

5.1.2. Adult IPAH and Healthy Groups

In the current study no significant differences were found between the two groups in terms of demographics. This shows comparability, except for age. The control healthy group showed higher 6MWD and pVO_2 values than the IPAH group despite being older. The existing literature describes a decrease in 6MWD and pVO_2 with an increase in age (Chetta, et al., 2006a; P. Enright & D. Sherrill, 1998; P. L. Enright & D. L. Sherrill, 1998a; K. e. a. Wasserman, 2012).

The reviewed literature shows age and gender as the variables affecting 6MWD the most (Casanova, et al., 2011), along with height and BMI in healthy adults (Soaresa & Pereira, 2011) (Kim et al., 2014). All available reference value equations for adults have also age, height, and gender, along with weight as variables that affect 6MWD. (Chetta, et al., 2006a; P. Enright & D. Sherrill, 1998; P. L. Enright & D. L. Sherrill, 1998a; Gibbons, Fruchter, Sloan, & Levy, 2001; Lee, Peacock, & Johnson, 2010; Troosters, Gosselink, & Decramer, 1999). Therefore differences

in those would have to be taken into account when comparing some of the groups. The most common reference value equation used is the Enright & D. Sherrill from 1998.

Age may be a limitation when comparing these two groups. It needs to be accounted for since age is a significant factor affecting 6MWD as well as performance (pVO_2) and any data related to oxygen consumption with exercise.

The differences found between groups in pVO_2 adjusted for body weight, as well as distance and walk speed were to be expected as VO_2 and distance are measurements of performance. It is expected to see better performance in healthy individuals when compared to diseased ones. Control normal subjects would be expected to have better cardiovascular fitness as expressed in higher peak VO_2 than diseased subjects.

Most of the differences found between these two groups are suggested by a difference in health status. In future investigations age control is suggested to better compare both adult groups.

5.1.3. IPAH Children and Healthy Children Group

There were no significant differences in height between the two groups. However significant differences were found in weight, BMI, and therefore speed and distance. Weight and BMI are related and both affect speed and ultimately distance. Higher BMI correlates with lower 6MWD (Klepper & Muir, 2011). However, despite the higher weight and BMI of the healthy children group the 6MWD was significantly higher for the control group.

It is understood the limitation of comparing a group of Spanish children (control group) against diseased American children. Studies performed in healthy Austrian, Swiss, Chinese, and Turkish children (Geiger, et al., 2007; Albert M. Li, et al., 2007; Ulrich, et al., 2013) were found but no

6MWT studies performed with Spanish children. However in the only study with American children (Klepper & Muir, 2011) demographics are almost identical in age, height, weight and BMI to the control group of the current study. Height, weight and BMI are the most important variables affecting 6MWD in children (Klepper & Muir, 2011). There is however a significant difference between the two groups in terms of 6MWD. The Spanish children control group may not be totally representative of American healthy children, however it could be representative of developed countries and it could be used to experiment with samples of healthy children that may not be existent. Age, height, weight, distance, and speed did not provide a large source of error in the healthy group. There was too much HR variability without normal distribution deeming that data unreliable, due to possible errors in the measurement of HR, therefore HR was not used.

It is suggested and expected that the main difference between the two groups was the health status or diagnosis of the subjects. In the future establishing health status based on 6MWD is suggested in children, especially younger, since it is an easier test than a CPET.

5.2. Study 2

Although differences on estimated VO_2 during 6MWT between healthy and IPAH individuals are to be expected, there is a lack of information on how much estimated oxygen uptake is used during a submaximal test like the 6MWT by these two groups. The findings in this study showed the true functional limitations of subjects with IPAH and how this limitations measure against healthy subjects.

Adult IPAH patients were found by calculation to be working at 55.6% of their peak oxygen consumption when walking for 6 minutes. This 55.6% of peak VO_2 reflects a significant amount of work, close to peak, in this population. Patients with IPAH have a moderate to severely reduced AT (R. J. Barst et al., 2004; G. E. D'Alonzo, et al., 1987; Miyamoto, et al., 2000; Sun, et al., 2001). The average at which AT occurs in relation to VO_2 maximum in normal individuals is roughly 50-60% (40-63% range when including different studies) of both $\text{VO}_{2\text{max}}$ and predicted $\text{VO}_{2\text{max}}$ (Hansen, Sue, & Wasserman, 1984; K. e. a. Wasserman, 2012). Therefore IPAH adult subjects when walking at 55.6% of peak VO_2 were working most likely above their AT. Meanwhile the adult control group at 43% of pVO_2 was working mostly below their AT.

Even though IPAH patients worked at a higher percent of their peak VO_2 there were no significant differences in reported Borg dyspnea score between IPAH and healthy groups. Perception of dyspnea appeared to be the same among healthy and IPAH subjects. This raises the question of whether the limitation on the 6MWT for IPAH population is something other than dyspnea. It is also suggested that IPAH subjects have a higher tolerance for dyspnea, since they are accustomed to being constantly dyspneic due to possible hyperventilation (Deboeck, et al., 2005).

The study found that IPAH patients were working at close to maximal rates while performing a 6MWT, but still at a lower VO_2 , as opposed to what was found on another study (Deboeck, et al., 2005). It is suggested that the difference between these two studies is that most of Deboeck's CPETs were completed before the 8-12 min recommended due to a possible over aggressive exercise protocol (10 W/min).

For better actual measurements the use of a validated (Díaz et al., 2008; Lucía, Fleck, Gotshall, & Kearney, 1993; J. E. McLaughlin, King, Howley, Bassett, & Ainsworth, 2001; Perret & Mueller, 2006; Rosdahl, Gullstrand, Salier-eriksson, Johansson, & Schantz, 2010) mobile gas analyzer to measure actual VO_2 achieved during the 6MWT as opposed to the calculated by ACSM formula, is recommended as been performed in healthy adults (Blanco et al., 2010; Deboeck, et al., 2005).

Validation of ACSM formula to calculate VO_2 during 6MWT is suggested since there appeared to be overestimation of VO_2 (Fegan, 1992; Filardo, da Silva, & Petroski, 2008). However, overestimation of VO_2 from ACSM formula would not affect the presented study since it would affect all groups equally.

A limitation of comparing METs and ADLS for different age groups is observed since energy expenditure seems to be higher in children than in adults (Harrell et al., 2005).

For future investigation it is suggested to test control groups of children and adolescents to compare with IPAH children and adolescents. In the future it is suggested that these compromised patients are trained under professional supervision (Grunig et al., 2011; Grunig, et al., 2012). Training would help patients with IPAH increase VO_2 and 6MWD which would translate into increase of quality of life and life expectancy (H. Groepenhoff, et al., 2008; Miyamoto, et al., 2000; Rhodes, et al., 1991; Wensel, et al., 2002). Increasing pVO_2 by training would translate into using less percentage of pVO_2 during a 6MWT. Therefore, patients would not be working at close to maximum levels and would be able to perform more ADLs at a lower energy cost (Ainsworth, et al., 2011). Based on same RPE scores between healthy and diseased

groups further exploration investigating the cause of limitation (leg fatigue, general fatigue?) for IPAH subjects is needed.

5.3. Study 3

The main result of the present study is that a simple 6MWT may be able to predict peak VO_2 in children with IPAH. However, the 6MWT may not be sufficient to predict peak VO_2 in most patients with IPAH. This is the first study that attempts to predict peak VO_2 from 6MWT solely in patients with IPAH. Being able to predict peak VO_2 from 6MWT would give physicians and health professionals an easy, inexpensive, and simple tool for the follow up of the disease. CPET requires the use of expensive equipment and trained medical team supervision to conduct and evaluate each test. Maximal exercise testing in IPAH populations involves a certain risk and requires well-trained and experienced health care professionals. The 6MWT was able to strongly predict peak VO_2 in children. However, the predictions were weaker in adolescents or adults.

Although peak VO_2 was predicted significantly ($r^2=0.83$) in the children group, peak VO_2 alone does not provide enough information for the treatment and prognosis of patients with IPAH. Peak VO_2 is only one of the many variables obtained during a CPET. Peak VO_2 would only show a decrease in fitness on these patients. It would, however, not determine the cause of the decrease. In children up to 12 years of age the 6MWT may be considered to predict peak VO_2 , although a previous CPET would always be highly recommended. The 6MWT test should be used as a follow up tool until adolescence.

Correlation between estimated VO_2 from CPET and 6MWT in healthy children (Limsuwan, Wongwandee, & Khowsathit, 2010) and correlation between CPET and 6MWT in patients with

IPAH (Oudiz et al., 2006a) has been shown by others. The correlation between 6MWT and measured VO_2 has not been shown. Ross et al. attempted to predict peak VO_2 from 6MWD in patients with different cardiopulmonary disorders, suggesting poor prediction accuracy for assessing individuals for clinical purposes (Ross, Murthy, Wollak, & Jackson, 2010). BMI and 6MWD were the only significant factors predicting peak VO_2 , in obese non adult patients. No coefficient of determination for the regression equation was cited (Vanelst, Vanelst, Fardy, Salleron, & Beghin, 2013). 6MWT does not seem to predict peak VO_2 in adult heart failure patients (Maldonado-Martin et al., 2006). Chuang et al. found that the Distance-Weight (DxW) product correlates with AT and $\text{VO}_{2\text{max}}$ and therefore it is a good tool to evaluate physical fitness when gas exchange is not available (Chuang, et al., 2001). However, no other study has tried to predict peak VO_2 from 6MWT in children, adolescents or adults with IPAH.

Weight, BMI, and height have been cited as the most important variables affecting 6MWD (Enright, 2003; P. L. Enright & D. L. Sherrill, 1998a, 1998b). These three variables demonstrate the strongest effect in the children's linear regression to predict peak VO_2 .

IPAH subjects showed, as expected, lower 6MWD than healthy patients from other studies: children with IPAH averaged 471.15 ± 89.43 meters vs 664 ± 65.3 meters (Albert M. Li, et al., 2007) and 619.2 ± 115.2 meters (Geiger, et al., 2007) in healthy children; adolescents with IPAH scored 455.78 ± 84.63 meters vs 699.2 ± 87 meters (Geiger, et al., 2007) found in healthy adolescents ; IPAH adults averaged a 6MWD of 459.77 ± 115.12 meters vs the distances averaged by other healthy adults of 615.5 ± 44 meters (Chetta, et al., 2006a) and 672 ± 83 meters (Ozasa et al., 2010).

Although a 6MWT may not be an instrument robust enough to predict peak VO_2 in adolescents and adults, it remains a very important tool to predict morbidity and mortality in a clinical setting. This tool is important in predicting shorter ICU stays after pediatric lung transplantation (Yimlamai, et al., 2013), as well as predicting morbidity and mortality in adult patients with left ventricular dysfunction (Bittner, et al., 1993). 6MWT is a significant predictor of survival in patients with IPAH (Benza, et al., 2010; Herman Groepenhoff, et al., 2013; Miyamoto, et al., 2000; Paciocco, et al., 2001; Timofte, et al., 2010). It is still used in clinical trials for IPAH medication use (Mathai, et al., 2012).

Although performing a simpler submaximal test like the 6MWT in children with IPAH may predict peak VO_2 it would not give health professionals the needed information to evaluate functional capacity. A simple 6MWT is not enough to predict peak VO_2 in most patients with pulmonary hypertension. It is however, an important tool for the evaluation and follow up of patients with IPAH.

The small sample size, specifically in the children group ($n=26$, with only 7 males) limits this study. For future research a larger sample size, at least in the children group, is needed. Such a sample size prevented us from validating the regression equations. Future studies comparing each group to a control group could shed more light on how and what prediction equations used in the study would apply to a normal or healthy population.

5.4. Study 4

This pilot study started to explore whether there would be any correlation between an invasive procedure (right heart catheterization) and a non invasive procedure (CPET). The current study

showed a slightly positive (0.32) average of individual correlations between mPAP and absolute pVO₂ but no correlation when comparing mPAP and adjusted pVO₂. On another note a slightly significant positive correlation was found between SBP and mPAP.

Percent predicted of VO₂ achieved has been inversely correlated to mPAP but not actual values of pVO₂ (Yasunobu, et al., 2005). Peak VO₂ has been used for prognosis and diagnosis in patients with IPAH, however no studies show mPAP as a prognostic value. The study shows no correlation between pVO₂ and mPAP which may suggest that mPAP has only a diagnostic value but not a prognostic one as a hemodynamic recording at rest.

Systolic blood pressure has been shown as a predictor of survival in patients with IPAH (Bersohn, Turner, Traiger, Frost, & Shapiro, 2013), but no correlation with mPAP has been established. It is important to note that peak systolic blood pressure is measured at peak exercise, while the mean pulmonary pressure is measured at rest. Correlation between SBP with exercise and mPAP during eRHC should be explored as recordings during exercise may be far more clinically relevant.

The results suggest that absolute or adjusted pVO₂ may not be able to predict mPAP. CPET may not be a substitute to right heart catheterization in order to measure pulmonary pressures. Other options need to be explored to find a surrogate for right heart catheterization. However, even if there was correlation between peak VO₂ and mPAP there would still be a need to perform right heart catheterization to get actual mPAP values and measurements in order to diagnose IPAH. Right heart catheterization still remains the gold standard in diagnosing IPAH. However more invasive and complex tests (such as RHC) cannot be repeated with the frequency and relative

low cost that CPET and 6MWT can be performed with. Therefore CPET still remains a good complement to right heart catheterization.

As a pilot study there are many limitations that need to be addressed in future investigations. Unfortunately, there was not enough data to draw significant comparisons or conclusions. Gathering more combined individual data of both mPAP and pVO₂ is suggested. There is the limitation of comparing a value obtained at rest (mPAP) with a value obtained at peak exercise (pVO₂). Future studies exploring the relation between VO₂ and PAP during exercise, possibly while performing an exercise right heart catheterization, are suggested (Provencher et al., 2008). Most exercise right heart catheterizations don't reach peak VO₂ levels. Instead these go up to approximately 80% of peak VO₂. For further consideration in these studies a submaximal exercise study while performing right heart catheterization is suggested. There are a few studies that measure simultaneously VO₂ and other gas exchange variables and PAP with exercise (Degani-Costa et al., 2015; Gregory D. Lewis, et al., 2013; G. D. Lewis et al., 2011). More studies of exercise right heart catheterization along with gas exchange measurements on the bike are suggested.

Future studies should also explore the relationship between non-invasive imaging techniques to evaluate right ventricular function, both at rest and during exertion (McCullagh & Girgis, 2010) with gas exchange variables from CPET.

5.5. General Discussion

This dissertation describes how exercise and exercise testing can be used to classify subjects with IPAH, measure their functional capacity, help in simplifying their lives, and possibly avoid

invasive testing. These studies also open new lines for investigation and briefly explore the use of exercise training as a beneficial tool for subjects with IPAH. The differences between IPAH groups and healthy subjects are within normal expectations due to the differences in health status. However, no significant differences were found between different groups regardless of their health status in terms of dyspnea.

IPAH subjects are compromised in their functional capacity as reflected by higher energy cost of 6MWT than healthy individuals which shows limitation on ADLs. Differences in functional status of IPAH subjects compared to healthy groups are significant regardless of other factors.

The attempts to simplify the lives of IPAH subjects by use of exercise were not completely successful. VO_2 max could be predicted from 6MWT in children but not for the entire IPAH population. However the studies bring up new avenues for the use of exercise testing and training as very important tools in the care of subjects with IPAH. Exercise testing can be a tool to simplify the lives of IPAH population, and it serves as a simple evaluation tool of their health status and functional capacity. Exercise can also be a part of the treatment for these patients.

6. CONCLUSIONS

6.1. Study 1

- There are no significant differences between IPAH groups. There are no differences in 6MWD between IPAH groups regardless of their age.
- Differences in exercise capacity were found between IPAH adults and healthy adult groups.
- Differences in exercise capacity were also found between IPAH children and healthy children.

Diseased patients have lower exercise capacity than healthy individuals regardless of the differences in demographics.

6.2. Study 2

- IPAH patients work at higher levels than normal subjects when performing 6MWT. IPAH children work at 69% of their pVO_2 and IPAH adolescents work at 63.5% of their pVO_2 when performing a 6MWT. Adults IPAH patients work at 55.6% of pVO_2 while healthy adults work at 43% of pVO_2 . However perception of dyspnea is the same between both groups.
- IPAH subjects have limited functional capacity for performing ADLs when compared to healthy subjects.

6.3. Study 3

- Peak VO_2 can be predicted from 6MWT in children (6-12 years old) with IPAH by linear regression equation. However, peak VO_2 cannot be predicted from 6MWT in older populations with IPAH with the same model.

6.4. Study 4

- Correlation between mPAP and pVO_2 was not found. CPET is not a substitute for right heart catheterization in patients with IPAH.

Right heart catheterization remains the gold standard for measuring mPAP and diagnosing patients with IPAH. However, CPET continues to be a good complement to right heart catheterization and as treatment of subjects with IPAH.

6.5. General Conclusions

Throughout this dissertation the characteristics of the specific IPAH population were described along with the characteristics of some normal groups. These different groups were compared to show the major differences in terms of exercise capacity (through 6MWT and CPET). The intention was also to demonstrate how these characteristics affect activities of daily living in patients with IPAH compared to normal subjects. The comparison between the healthy adult group and the adult group with IPAH proves how IPAH patients are working harder and are more limited while performing activities of daily living. This work grew out of the idea of using exercise and exercise testing to make life easier for those living with a disease like IPAH. Thus, it was hypothesized that oxygen consumption could be predicted from 6MWT. Predicting oxygen consumption from a 6MWT would be of great help in places where access to CPET and gas analyzers may not be available, or for people who may not have the appropriate means

(insurance, coverage, funds, etc.). Simplifying the lives of these subjects by the use of exercise testing was also the motivation for the study correlating pulmonary pressures with CPET (Rhodes, et al., 1991). If mPAPs were able to be correlated (and eventually predicted) with pVO_2 and pVO_2 could be predicted from 6MWT, eventually a complicated invasive test such as a right heart catheterization could be simplified in the form of an exercise test such a CPET or a 6MWT. This would not only simplify the lives of patients with IPAH, but it would also give hope for providing better care to these patients in places where the means to treat the disease are limited. Pulmonary pressures could not be correlated to CPET measurements in this study; therefore more research may be needed in this field. Exercise testing and exercise training presently remain and can remain in the future as important resources in clinical testing of IPAH and other diseased populations.

Finding simpler ways to diagnose, treat, and care for these subjects should be a goal of those involved in patient care. Thus, the use of exercise can play a very important role in the treatment of IPAH and other diseases.

7. LIMITATIONS AND FUTURE LINES OF INVESTIGATION

There are certain limitations to the studies proposed in this dissertation. There are the limitations of comparing groups of children from different demographics (Spain vs. US) and adults with significant age differences. There is a need to study in more detail some of the groups, such as the children group to gather more valuable data as well as to gather predicted values. In the future it would also be helpful to have children and adolescent control groups, so the IPAH groups could be compared to normal populations of those groups. A comparison of children and adolescent IPAH groups with healthy groups would show whether levels of exertion vary with age or whether they are more dependent on health status. There are limitations on using an equation to predict VO_2 consumption during 6MWT as opposed to measuring direct oxygen consumption with a mobile gas analyzer. An increased sample size when predicting VO_2 from 6MWT would give the study more significance. There is also a need to validate the prediction equation with an independent t sample. This is one of the first studies that explores correlation between non invasive CPET and invasive measurement of pulmonary pressures. There may be very important benefits from exploring correlation and eventually prediction of invasive measurements from non invasive exercise testing. This approach could open up options and could help with treatments of subjects with IPAH.

Heart rate measurement was a source of error when collected during the 6MWT in the Spanish school children group. In order to account for this error it is suggested to use a heart rate monitor to improve accuracy in the data collection process.

More studies on exercise training in patients with IPAH are suggested to measure improvement in exercise capacity and quality of life. It has been suggested that exercise can improve the outcome, prognosis and life of patients with IPAH.

In order to decrease the amount of right heart catheterization, since it carries a substantial risk, exercise right heart catheterization with measurement of gas exchange variables is suggested. This approach could be very beneficial in prevention with patients who start with exercise induced IPAH. Further exploration of this possibility could yield important information on prediction of PAP as well as other important variables. Comparing oxygen consumption and other indirect calorimetry measurements with pulmonary pressures could be of great benefit to the treatment of these patients.

This is a comprehensive study on how exercise, exercise testing, and training can help in the treatment, prognosis, and diagnosis of IPAH. This dissertation opens up a very important perspective. Exercise testing and exercise training are important factors that may make life easier for diseased subjects. This approach could be applied to other diseases. Exercise and exercise testing could and should be a part of the comprehensive care of patients not only with IPAH but with any disease.

8. FINAL THOUGHTS

Throughout the text a picture of the exercise capacity and functional capacity of IPAH population has been given and how it compares to a normal population. Exercise testing and training have been established as important resources for subjects with IPAH. Exercise in the form of testing, such as 6MWT and CPET, has been proven to be an important tool in the treatment of IPAH population. Exercise training has also been explored as a possible tool that may be used to improve quality of life in these subjects. Studying the application of exercise in this specific population opens a wide array of possibilities in the health care and medical fields. Thus, an integration of health care and exercise fields is not only beneficial but necessary in order to move forward in the care and treatment of IPAH patients and other diseased populations. The possibilities, advantages, contributions, and applications of exercise in healthcare are endless. It is our duty, as exercise physiologists and exercise professionals, to continue exploring these possibilities.

9. APPENDIXES

Appendix A

CPET Summary

	<u>Rest</u>	<u>AT</u>	<u>V02 Max</u>	<u>Pred</u>	<u>V02 Max/Pred (%)</u>
—FUNCTIONAL CAPACITY—					
VO2 (mL/kg/min)	3.7	43.4	52.2	36.6	143
VO2 (L/min)	0.27	3.23	3.89	2.72	143
VCO2 (L/min)	0.36	3.29	4.05	3.29	123
Work (Watts)	0	250	250	212	118
METS	1.0	12.4	14.9	10.5	142
Borg PE					
Time (min)	2:40	14:00	17:40		
—CARDIOVASCULAR RESPONSE—					
HR (BPM)	81	167	185	182	102
sysBP (mmHg)	131	172	176		
diaBP (mmHg)	93	98	94		
HRR (BPM)	101	15	-3		
VO2/HR (mL/beat)	3.4	19.3	21.0	15.0	140
Delta VO2/Watts (L/Min/Watt)					
—VENTILATORY RESPONSE—					
VE BTPS (L/min)	15	86	136	215	63
BR (%)	93	60	37		
Vt BTPS (L)	1.12	2.83	3.76		
RR (br/min)	13	30	36		
VE/MVV (%)	7	40	63		
Vt/IC (%)	27	70	92		
—GAS EXCHANGE—					
PETCO2 (mmHg)	30	41	33		
PETO2 (mmHg)	124	109	117		
VE/VCO2	41	26	34	46	74
VE/VO2	54	27	35	55	63
Vd/Vt - est	0.25	0.08	0.04		
RER	1.32	1.02	1.04		
SpO2 (%)	100	96	96		
— V/Q —					
P(A-a)O2 (mmHg)					
Vd/Vt - meas					

Appendix B

Wasserman panel 9 (K. e. a. Wasserman, 2012)

Appendix C

CPET Data display (20 second average)

Time (min)	Work (Watts)	HR (BPM)	VO2 (L/min)	VCO2 (L/min)	RR (br/min)	VO2 (mL/kg/min)	VO2/HR (mL/beat)	VE (L/min)	Vt (L)	RR (br/min)	VE/VO2 (L/L)	PETCO2 (mmHg)
0:20	0	73	0.82	0.75	0.91	11.0	11.2	24	1.72	14	29	32
0:40	0	68	0.41	0.41	1.00	5.5	6.0	15	0.89	16	36	36
1:00	0	85	0.75	0.74	0.98	10.1	8.9	22	1.53	14	29	37
1:20	0	78	0.42	0.50	1.20	5.6	5.3	17	1.74	10	40	33
1:40	0	74	0.33	0.39	1.17	4.5	4.5	13	1.40	9	39	33
2:00	0	71	0.32	0.36	1.13	4.3	4.5	11	1.87	6	36	31
2:20	0	72	0.44	0.51	1.17	5.9	6.1	17	2.75	6	40	34
2:40	0	81	0.27	0.36	1.32	3.7	3.4	15	1.12	13	54	41
Start												
3:00	50	77	0.62	0.61	0.98	8.4	8.1	18	1.38	13	30	30
3:20	50	99	0.87	0.90	1.04	11.7	8.8	29	2.42	12	33	32
3:40	50	99	0.96	0.95	1.00	12.9	9.7	27	2.01	14	29	29
4:00	50	97	0.88	0.86	0.97	11.9	9.1	25	2.00	12	28	29
4:20	50	95	0.99	0.88	0.89	13.4	10.5	24	2.08	12	24	27
4:40	50	96	0.96	0.85	0.89	12.9	10.0	23	2.20	11	24	27
5:00	50	92	0.95	0.83	0.88	12.7	10.3	23	2.11	11	24	28
5:20	50	90	0.93	0.81	0.87	12.6	10.4	23	1.95	12	24	28
5:40	50	92	0.96	0.84	0.87	12.9	10.4	23	2.26	10	24	27
6:00	50	93	1.07	0.99	0.92	14.4	11.5	29	2.79	10	27	29
6:20	50	94	1.01	0.94	0.93	13.6	10.8	27	2.64	10	27	29
6:40	50	88	0.90	0.86	0.96	12.0	10.2	24	2.18	11	27	29
7:00	50	89	0.85	0.73	0.85	11.5	9.6	20	1.68	12	24	28
7:20	50	91	1.06	0.93	0.87	14.3	11.7	25	2.46	10	24	28
7:40	50	92	0.93	0.81	0.87	12.5	10.1	23	1.67	14	24	28
8:00	150	93	0.90	0.74	0.82	12.2	9.7	20	1.30	16	23	27
8:20	150	108	1.45	1.14	0.79	19.4	13.4	28	2.13	13	20	25
8:40	150	113	1.58	1.42	0.90	21.3	14.0	35	2.59	14	22	25
9:00	150	120	1.94	1.72	0.89	26.1	16.2	41	1.99	20	21	24
9:20	150	122	1.96	1.91	0.98	26.3	16.0	45	2.17	21	23	24
9:40	150	126	2.05	2.05	1.00	27.5	16.3	48	2.53	19	23	23
10:00	150	126	2.14	2.19	1.02	28.7	17.0	53	2.31	23	25	24
10:20	150	127	2.13	2.22	1.04	28.7	16.8	54	2.65	20	25	24
10:40	150	132	2.16	2.24	1.04	29.0	16.4	55	2.63	21	25	24
11:00	150	133	2.35	2.33	0.99	31.6	17.7	58	2.39	24	25	25
11:20	150	130	2.22	2.23	1.00	29.8	17.1	57	2.60	22	26	26

Time (min)	Work (Watts)	HR (BPM)	VO2 (L/min)	VCO2 (L/min)	RER	VO2 (mL/kg/min)	VO2/HR (mL/beat)	VE (L/min)	BTPS Vt (L)	RR (br/min)	VE/VO2	VE/VCO2	PEtCO2 (mmHg)
11:40	150	138	2.32	2.24	0.97	31.2	16.8	57	2.35	24	25	26	42
12:00	150	135	2.41	2.27	0.94	32.4	17.9	55	2.66	21	23	24	44
12:20	150	135	2.38	2.27	0.95	32.0	17.6	57	2.47	23	24	25	42
12:40	150	139	2.45	2.29	0.94	32.9	17.6	58	2.42	24	24	25	42
13:00	250	140	2.56	2.41	0.94	34.5	18.3	63	2.36	27	25	26	41
13:20	250	151	2.73	2.65	0.97	36.7	18.1	70	2.84	25	26	27	41
13:40	250	159	3.06	2.93	0.96	41.1	19.2	75	2.61	29	25	26	42
AT													
14:00	250	167	3.23	3.29	1.02	43.4	19.3	86	2.83	30	27	26	41
14:20	250	171	3.32	3.48	1.05	44.6	19.4	91	3.13	29	27	26	41
14:40	250	163	3.39	3.67	1.08	45.6	20.8	99	3.39	29	29	27	40
15:00	250	173	3.47	3.73	1.07	46.6	20.1	103	3.22	32	30	28	39
15:20	250	179	3.58	3.92	1.09	48.2	20.0	113	3.51	32	32	29	38
15:40	250	181	3.59	3.95	1.10	48.3	19.8	116	3.54	33	32	29	37
16:00	250	182	3.67	4.01	1.09	49.4	20.2	121	3.80	32	33	30	37
16:20	250	183	3.72	3.98	1.07	50.0	20.3	120	3.75	32	32	30	36
16:40	250	185	3.83	4.06	1.06	51.5	20.7	128	3.53	36	33	32	35
17:00	250	186	3.83	4.07	1.06	51.5	20.6	131	3.64	36	34	32	34
17:20	250	187	3.82	4.03	1.05	51.3	20.4	132	3.72	36	35	33	33
V02													
17:40	250	185	3.89	4.05	1.04	52.2	21.0	136	3.76	36	35	34	33
18:00	0	177	3.72	3.82	1.03	50.1	21.0	134	3.25	41	36	35	31
18:20	0	179	2.77	3.14	1.13	37.2	15.5	113	3.35	34	41	36	31
18:40	0	165	2.01	2.70	1.35	27.0	12.2	100	3.17	32	50	37	30
19:00	0	154	1.39	1.95	1.40	18.7	9.0	68	3.11	22	49	35	32
19:20	0	143	1.24	1.70	1.36	16.7	8.7	60	2.24	27	48	36	31
19:40	0	132	1.16	1.63	1.40	15.6	8.8	61	2.54	24	53	38	29
20:00	0	128	1.00	1.32	1.33	13.4	7.8	50	2.00	25	50	38	30
20:20	0	121	0.98	1.29	1.32	13.2	8.1	48	2.56	19	49	37	29
20:40	0	117	0.82	1.00	1.21	11.0	7.0	36	1.48	24	44	36	30
21:00	0	117	0.87	1.04	1.19	11.7	7.4	39	1.73	23	45	38	29
21:20	0	113	0.85	1.03	1.20	11.5	7.6	39	1.77	22	45	38	29
21:40	0	112	0.77	0.84	1.10	10.3	6.8	31	1.31	23	40	37	30
21:47	0	121	0.85	0.90	1.06	11.5	7.0	34	1.04	33	40	38	29

Appendix D 6MWT Data collection form

MORGAN STANLEY CHILDRENS HOSPITAL OF NEW YORK PRESBYTERIAN
PEDIATRIC CARDIOPULMONARY EXERCISE LABORATORY

SIX MINUTE WALK TEST

Name: _____

Date: _____

Distance of one length: 30 meters

Start time: _____ AM/PM

Protocol: _____

End time : _____ AM/PM

Number of rests: _____

Symptoms: _____

Did the patient walk the entire six minutes? Yes No

Was supplemental oxygen in use during the walk test? Yes No Level _____

SpO2 before walk test (HR): _____ % (_____) SpO2 after walk test (HR): _____ % (_____)

Borg Dyspnea Score : _____ Total Distance walked: _____ meters

Tally Box		0	Nothing at all
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;">Number of Rest</div> <div style="width: 45%;">Time of Rest</div> </div>		0.5	Very, Very slight (just noticeable)
		1	Very Slight
		2	Slight
		3	Moderate
		4	Somewhat Severe
		5	Severe
		6	
		7	Very Severe
		8	
		10	Maximal

Appendix E 6MWD predicted equations

6MWD Predicted Equation	Male	Female
<i>ENRIGHT 1998 USA; 117 males, 173 females; age 40–80 yrs</i>	$(7.57 \times H_{\text{tcm}}) - (5.02 \times \text{age}) - (1.766 \times W_{\text{tkg}}) - 309m$	$(2.11 \times H_{\text{tcm}}) - (5.78 \times \text{age}) - (2.29 \times W_{\text{tkg}}) + 667m$
<i>TROOSTERS 1999 Belgium; 29 males, 22 females; age 50–85 yrs</i>	$218 + (5.14 \times H_{\text{tcm}}) - (5.32 \times \text{age}) - (1.8 \times W_{\text{tkg}}) + (51.31 \times 1)$	$218 + (5.14 \times H_{\text{tcm}}) - (5.32 \times \text{age}) - (1.8 \times W_{\text{tkg}}) + (51.31 \times 0)$
<i>GIBBONS 2001 Canada; 41 males, 38 females; age 20–80 yrs</i>	$868.8 - (\text{age} \times 2.99) - (0 \times 74.7)$	$868.8 - (\text{age} \times 2.99) - (1 \times 74.7)$
<i>CHETTA 2006 Italy; 48 males, 54 females; age 20–50 yrs</i>	$518.853 + (1.25 \times H_{\text{tcm}}) - (2.816 \times \text{age}) - (39.07 \times 0)$	$518.853 + (1.25 \times H_{\text{tcm}}) - (2.816 \times \text{age}) - (39.07 \times 1)$
Children predicted equations (3–18 years old) (Geiger, et al., 2007)	$196.72 + (39.81 \cdot \text{Age}) - (1.36 \cdot \text{Age}^2) + (132.28 \cdot \text{Heightcm})$	$188.61 + (51.50 \cdot \text{Age}) - (1.86 \cdot \text{Age}^2) + (86.10 \cdot \text{Heightcm})$

Appendix F Activities of Daily Living (ADLs) by MET level

MET		Activity
0.95	inactivity quiet/light	sleeping
1	inactivity quiet/light	lying quietly and watching television
2	conditioning exercise	yoga, Nadisodhana
		cooking or food preparation - standing or sitting or in general (not broken into stand/walk components), manual appliances,
2	home activities	light effort
		laundry, fold or hang clothes, put clothes in washer or dryer, packing suitcase, washing clothes by hand, implied standing,
2	home activities	light effort
		scrubbing floors, on hands and knees, scrubbing bathroom,
2	home activities	bathtub, light effort
2	home activities	standing, light effort tasks (pump gas, change light bulb, etc.)
2	home activities	standing, holding child
		child care, sitting/kneeling (e.g., dressing, bathing, grooming,
2	home activities	feeding, occasional lifting of child), light effort, general
2	home activities	breastfeeding, sitting or reclining
2	self care	showering, toweling off, standing
2	walking	walking, household
2	walking	walking, less than 2.0 mph, level, strolling, very slow

2.3	home activities	cleaning, sweeping, slow, light effort
2.3	home activities	dusting or polishing furniture, general
		food shopping with or without a grocery cart, standing or
2.3	home activities	walking
2.3	home activities	non-food shopping, with or without a cart, standing or walking
		laundry, putting away clothes, gathering clothes to pack,
2.3	home activities	putting away laundry, implied walking
		walking and carrying small child, child weighing less than 15
2.3	home activities	lbs
2.3	occupation	postal carrier, walking to deliver mail
2.5	conditioning exercise	yoga, Hatha
2.5	home activities	mopping, standing, light effort
2.5	home activities	feeding household animals
2.5	occupation	cook, chef
2.5	occupation	police, directing traffic, standing
2.5	occupation	police, driving a squad car, sitting
2.5	self care	dressing, undressing, standing or sitting
2.5	sports	football or baseball, playing catch
		walking from house to car or bus, from car or bus to go places,
2.5	walking	from car or bus to and from the worksite
2.8	conditioning exercise	upper body exercise, arm ergometer
2.8	home activities	sewing with a machine

3	conditioning exercise	pilates, general
		ballroom, slow (e.g., waltz, foxtrot, slow dancing, samba,
3	dancing	tango, 19th century dance, mambo, cha cha)
		walking and carrying small child, child weighing 15 lbs or
3	home activities	more
3	lawn and garden	riding snow blower
3	occupation	airline flight attendant
3	occupation	kitchen maid
3	occupation	locksmith
3	walking	walking the dog
3	walking	Children PH 6MWT
3.1	walking	Adolescents PH 6MWT
3.1	walking	Adults PH 6MWT
3.2	home activities	cleaning windows, washing windows, general
3.3	home activities	cleaning, sweeping carpet or floors, general
3.3	home activities	making bed, changing linens
3.3	home repair	painting inside house, wallpapering, scraping paint
		carrying, loading or stacking wood, loading/unloading or
3.3	lawn and garden	carrying lumber, light-to-moderate effort
3.3	occupation	electrical work (e.g., hook up wire, tapping-splicing)
3.3	sports	lawn bowling, bocce ball, outdoor
3.5	bicycling	bicycling, leisure, 5.5 mph

		cleaning, heavy or major (e.g. wash car, wash windows, clean garage), moderate effort
3.5	home activities	standing, packing/unpacking boxes, occasional lifting of lightweight household items, loading or unloading items in car,
3.5	home activities	moderate effort
3.5	lawn and garden	weeding, cultivating garden, light-to-moderate effort
3.5	transportation	motor scooter, motorcycle
3.5	water activities	swimming, treading water, moderate effort, general
4	walking	Adult control 6MWT
4	conditioning exercise	yoga, Power
4	home activities	sweeping garage, sidewalk or outside of house
4	lawn and garden	sacking grass, leaves
4	lawn and garden	trimming shrubs or trees, manual cutter
4	occupation	massage therapist, standing
4	sports	coaching, football, soccer, basketball, baseball, swimming, etc.
4.4	exercise	Children PH VO ₂ peak
5	exercise	Adolescents PH VO ₂ peak
5	dancing	ballet, modern, or jazz, general, rehearsal or class
5	home repair	cleaning gutters
		mowing lawn, walk, power mower, moderate or vigorous effort
5	lawn and garden	effort
5	lawn and garden	weeding, cultivating garden, using a hoe, moderate-to-vigorous

		effort
5.6	exercise	Adults PH VO ₂ peak
6	conditioning exercise	rowing, stationary ergometer, general, vigorous effort
6	home repair	carpentry, sawing hardwood
6	home repair	roofing
6	lawn and garden	mowing lawn, walk, hand mower (Taylor Code 570)
6	lawn and garden	shovelling snow, by hand (Taylor Code 610)
6	lawn and garden	yard work, general, vigorous effort
6	sports	skateboarding, competitive, vigorous effort
7	conditioning exercise	bicycling, stationary, general
7	winter activities	skiing, general
7.5	home activities	carrying groceries upstairs
8	occupation	carrying heavy loads (e.g., bricks, tools)
8	occupation	fire fighter, general
8	running	jogging, in place
		steel mill, vigorous effort (e.g., hand rolling, merchant mill
8.3	occupation	rolling, removing slag, tending furnace)
8.5	bicycling	bicycling, mountain, general
9	sports	horseback riding, jumping
9.3	exercise	Adult control VO ₂ peak
9.3	sports	basketball, drills, practice
10	running	running, on a track, team practice

10	sports	soccer, competitive
10	water activities	water polo
11	water activities	windsurfing or kitesurfing, crossing trial
13.3	running	running, marathon
13.8	water activities	swimming, butterfly, general
14	winter activities	skating, ice dancing
15	running	running, stairs, up
16	bicycling	bicycling, mountain, competitive, racing
		forestry, ax chopping, very fast, 1.25 kg axe, 51 blows/min,
17.5	occupation	extremely vigorous effort
19	running	running, 12 mph (5 min/mile)
23	running	running, 14 mph (4.3 min/mile)

Appendix G Consent Form

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAA0599

Principal Investigator: Robert Garofano

(rpg13)

IRB Protocol Title: A Study of Measured Oxygen Consumption during the Six-Minute Walk Test in Patients with Pulmonary Arterial Hypertension

Consent Number: CF-AAAL0338

Participation Duration: 1 hour

Anticipated Number of Subjects: 144

Contact

Contact	Title	Contact Type	Numbers
Erika Berman-Rosenzweig	Asst Prof	Emergency	Telephone: 212-305-4436
Robert Garofano	Asst Clin Prof	Principal Investigator	Telephone: 212-305-7850

Research Purpose

The purpose of this study is to find out the effect of pulmonary hypertension on oxygen use during exercise testing.

Additional Information

Statement of the Research

You or your child are invited to participate in a research study.

The purpose of this consent form is to provide you with the information that you need to decide whether to participate in this research study and to inform you, as completely as possible, of the nature, purpose and risks involved in the study.

The Principal Investigator, or authorized member of the study team will explain to you the purpose of the project study, the procedures to be used, and the potential benefits and risks of your participation.

Please ask the investigator or study team member to explain anything that you do not understand.

The consent form is your record of what was discussed, and informs you of your rights as a participant in this research. We ask that you read this consent form completely and ask any questions you may have before agreeing to participate in the study. Do not sign this consent form unless you have received satisfactory answers to all of your questions. You will be given a copy of the consent form to keep.

Printed On: 10/01/2007 at 14:12 page 1 of 5

Information on Research

Study Purpose:

You or your child are invited to participate in a research study of the effect of pulmonary hypertension on exercise testing.

You or your child qualify as a possible participant in this study because you or your child do not have pulmonary hypertension and will therefore serve as a "control group;" that is, normal subjects with whom we will compare patients with pulmonary hypertension. The purpose of this study is to evaluate the effect of pulmonary hypertension on oxygen use during the six minute walk test and bicycle exercise test. We believe that people with pulmonary hypertension use more oxygen during these tests than people without pulmonary hypertension such as you or your child.

Study Procedures:

If you or your child choose to participate, you or your child will be asked to complete a six-minute walk and a exercise test on a bicycle while wearing a device that will measure oxygen use.

For the six-minute walk, you or your child will be asked to walk as much as possible, back and forth, in a hallway for six-minutes. You or your child may stop at any time. The device involves placement of a mask over the mouth and nose that is held in place by elastic straps attached to a skull cap. To measure breathing, there is a strap on the chest to hold a small machine that weighs 650 grams (approximately 1 pound, 6 ounces).

For the bicycle test, you or your child will be asked to pedal a stationary bicycle for as long as you can while the work level is slowly increased. The usual duration for an exercise test is between 7 to 12 minutes. There will be a warm-up period of 3 minutes before the test, and a cool-down period of 10 minutes after the test. You or your child may stop at any time. Your heartbeat and blood pressure will be monitored throughout the test. You or your child will wear a mouthpiece that is connected to a machine to measure oxygen use, and a nose clip.

The total duration of time for these tests will require approximately one hour. The tests may occur in any order.

Risks

You or your child's participation in this study adds no additional risk to that already associated with exercise. These risks are muscle strain or injury, an abnormal heart beat, and rarely fainting. The approximate incidence of these risks are less than 1/10,000 for adults, and probably lower in children.

Benefits

Involvement in this study is not intended to benefit you or your child personally. However, if you or your child are interested, you will be able to learn the results of the exercise tests. The results of these tests include information on your or your child's ability to exercise. You or your child will be informed of any significant results from participation in this study. Benefits to society may include advancing the understanding of heart and lung function in people with pulmonary hypertension once the study is completed.

Alternative Procedures

The alternative is not to participate in this research study.

Additional Information

Confidentiality

Although every effort will be made to protect the confidentiality of your records, absolute confidentiality cannot be guaranteed. By signing this document you grant permission for information about you obtained during the study to be made available to:

- The investigator, study staff and other health professionals who may be evaluating the study;
- Columbia University;
- New York Presbyterian Hospital; -

Authorized representatives of the Office of Human Research Protections ("OHRP") or other government regulatory agencies (if applicable); and

-Applicable Institutional Review Boards ("IRBs") that independently review the study to assure adequate protection of research participants, as required by federal regulations.

The investigator, regulatory authorities, IRB and study sponsor may keep the research records indefinitely. If the results of the study are published or presented at a medical or scientific meeting, you will not be identified. An Institutional Review Board is a committee organized to protect the rights and welfare of human subjects involved in research.

Research Related Injuries

Research Related Injuries

If you or your child are injured as a result of you or your child's involvement in this study, Columbia Presbyterian Hospital will furnish emergency care and assistance in arranging follow-up care determined to be necessary by its medical staff. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage. You should be aware that insurance companies sometimes will not pay for research related injuries in which case you will be charged. There should be no expectation that Columbia University will pay for research related injuries. No monetary compensation for wages lost as a result of injury will be paid to you by the Columbia Presbyterian Hospital. However, you should be aware that participation in this study does not waive any of you or your child's legal rights to seek such compensation through the courts.

Additional Information

Questions

If you have any questions or concerns about the study, you may contact the Principal Investigator, Robert P. Garofano 212-305-7850, or the emergency contact person, Erika B. Rosenzweig 212-305-4436. If you have any questions about your rights as a subject, you may contact:
Health Sciences Institutional Review Board
Columbia University Health Sciences
722 West 168th Street, 4th Floor
New York, NY 10032

Telephone: (212) 305-5883

Voluntary Participation & Early Withdrawal

Your participation in the study is voluntary. You may decide not to participate in the study. If you decide to participate, you are free to withdraw from the study at any time. Your refusal to participate, or your early withdrawal, will not affect any benefits to which you are otherwise entitled from Columbia University or the Sponsor.

Compensation

You or your child will not receive any payment or other compensation for participating in this study.

Additional Costs

There are no costs to you or your child for participating in this study.

Additional Information

Statement of Consent

I voluntarily consent to participate in the study. I have thoroughly read this consent form and understand the nature and the purpose of the study.

I have fully discussed the study with the investigator or study staff, have had the opportunity to ask questions and have received satisfactory answers. The explanation I have been given has mentioned both the possible risks and benefits to participating in the study and the alternatives to participation.

I understand that I am free to not participate in the study or to withdraw at any time. My decision to not participate or to withdraw from the study will not affect my future care or status with this investigator.

I confirm that I have informed the investigator or study staff to the best of my knowledge of: any medication/drug that I have taken in the month before the start of the study; and any medication/drug that I am taking or plan to take, whether prescribed or not. I agree to cooperate with the study investigator/staff and will report any unexpected or unusual symptoms.

I understand that I will receive and may keep a copy of this signed and dated consent form. By signing and dating this consent form, I have not waived any of the legal rights that I would have if I were not a participant in the study.

Signature

Study Participant

Print Name _____ Signature _____ Date _____

Parent/Guardian

Print Name _____ Signature _____ Date _____

Person Obtaining Consent

Print Name _____ Signature _____ Date _____

Medical Center Institutional Review Board: 212-305-5883
Consent Form #: CF-AAAL0338 Copied From: CF-AAAK3137
Printed On: 10/26/2012 at 12:01 page 5 of 5

Columbia University IRB

IRB Approval Date: 06/21/2012
for use until: 06/20/2013

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EDUCATION

Doctor of Science in Sport and Physical Activity, ABD, Exercise Physiology, Expected 2016
Universidad Politecnica de Madrid, Madrid, Spain

Masters of Arts in Applied Physiology, May 2008
Columbia University Teachers College, New York, NY

Bachelor of Science in Education, December 2003
Northern Illinois University, DeKalb, Illinois
Major: **Sport Management**

Bachelor and Masters of Science in Education, May 2000
Universidad Politecnica, Madrid, Spain
Major: **Physical Education/Exercise Science**

Teaching Certificate, May 2000
Universidad Complutense, Madrid, Spain

Certified Pulmonary Function Technologist: National Board for Respiratory Care, August 19 2013- August 31 2018

PROFESSIONAL EXPERIENCE

Lead Exercise Physiologist/Pulmonary Technologist, Pulmonary Laboratories, Pulmonary & Critical care Medicine, University of Michigan Health System, Ann Arbor, MI, October 2014-present
Conduct Pulmonary Function and Cardiopulmonary Exercise Tests at both clinical and research level
Responsible for clinical and research exercise studies and interpretations
Responsible for teaching and training fellows, medical students, and new employees
Member of Quality Assurance, Educational, Calibration and many other committees

Exercise Physiologist, Preventative Cardiology, Cardiovascular Medicine, University of Michigan Health System, Ann Arbor, MI, March-October 2014
Conducted stress tests, clinical cardiopulmonary exercise test, EECPP
Supervised Phase III Cardiac Rehabilitation
Interpreted stress tests and cardiopulmonary exercise tests

Senior Specialist in Cardiopulmonary Exercise Physiology and Pulmonary Function, Children's Hospital of New York Presbyterian-Columbia University Medical Center, New York, NY, 2008-March 2014
Conducted and performed different cardiopulmonary research and clinical studies
Assisted supervisor with billing, budgeting, scheduling, compliance, and quality assurance
Trained new techs and interns

Swimming Head Coach, Somerset Dolphins Swim Team, Town of Somerset, Chevy Chase, MD, Summers 2004-2007
Managed a team of 5 assistant coaches and 125 swimmers

Marketing Assistant, Department of Marketing and Sports Promotions. Northern Illinois University, DeKalb, IL, USA, 2003
Handled Group tickets, helped in designing and creating entries and calendars
Created and distributed flyers and promotional material and marketing

Supervisor, Dining Services of Northern Illinois University, DeKalb, IL, USA August 2002-December 2003
Promoted to supervisor in one semester
Supervised a group of 6-8 employees in different aspects of the restaurant service
Maintained efficient customer service

Organizer and Coordinator of Sports Events, Athletic Department, Northern Illinois University, DeKalb, IL, USA August 2002-December 2003

Helped in setting up and organizing attendance at sporting events for various sports (football, basketball, swimming, volleyball, etc.),
Organized and conducted sports events in different facilities and stadiums

Administrative Assistant, Office of Student Athlete, Intercollegiate Athletics Department, Northern Illinois University, DeKalb, IL, USA, August-December 2002

Helped administrative staff
Analyzed data
Tutored student athletes

SPECIAL SKILLS

Computer: MS Word, Excel, PowerPoint

Language: Spanish (bilingual), English (bilingual)

AWARDS

2001 Swimmer of the year, Northern Illinois University Swimming and Diving team

Victory Scholar 2000, 2001, 2002, 2003 (Awarded to those student athletes with a 3.5 or higher GPA)

National Champion 50 M Freestyle, Spanish National Championships, Zaragoza, July 2000

PUBLICATIONS

Fuentes, D., Zapico, A., Calderon, F.J., Rosenzweig, E.B., Rojo-Tirado, M.A., Garofano, R. P. *Predicting $VO_{2\text{ peak}}$ from Six Minute Walk Test in Patients with Pulmonary Hypertension.*

ACSM 61st Annual meeting 5th World congress on Exercise is Medicine, Orlando, Florida, 2014 Abstract accepted.

Fuentes, D., Zapico, A., Calderon, F.J., Rosenzweig, E.B., Rojo-Tirado, M.A., Garofano, R. P. *Predicting $VO_{2\text{ peak}}$ from Six Minute Walk Test in Patients with Pulmonary Hypertension.*

Target Journal: Journal of Cardiopulmonary Rehabilitation and Prevention. Manuscript accepted.

Fuentes, D., Zapico, A., Calderon, F.J., Rosenzweig, E.B., Garofano, R. P. *Exercise Testing in Pulmonary Hypertension: A review.*

Target Journal: Chest. Manuscript in preparation

Fuentes, D., Zapico, A., Calderon, F.J., Rosenzweig, E.B., Rojo-Tirado, M.A., Garofano, R. P. *Functionality of Patients With Pulmonary Hypertension: A pilot study.*

Target Journal: International Journal Of Sports Medicine. Manuscript in preparation

Carvajal M. Ramos, **D. Fuentes Sánchez**, Santiago Martín-Sonsec G., López Menéndez, C. (2010). *Lytic lesion in skull*. Family Physicians. 3 (11) :25-6