

**IS THERE A RELATIONSHIP BETWEEN CHANGE IN DISEASE SEVERITY
AND CHANGE IN GAS EXCHANGE DURING A SIX-MINUTE WALK TEST IN
PATIENTS WITH IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION?**

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA

BY:

Monika Sattler

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF:

Master of Science

ADVISOR: Eric M. Snyder, Ph.D.

May 2014

Copyright Page

© Monika Sattler 2014. All rights reserved.

ACKNOWLEDGEMENTS

This research was conducted at Prince Charles Hospital, Brisbane, Australia.

The following thesis would not have been possible without the generous guidance of Dr. Eric Snyder (University of Minnesota, USA) and Dr. Norman Morris (Griffith University, AUS), Dr. Don Dengel (University of Minnesota, USA) and Dr. George Biltz (University of Minnesota, USA) as well as the help of Helen Seale (Prince Charles Hospital, Brisbane, AUS) and Kathleen Hall (Prince Charles Hospital, Brisbane, AUS).

ABSTRACT

The aim of this pilot study was to determine if there was a relationship between disease severity, measured by right ventricular systolic pressure (RVSP), and gas exchange, measured by oxygen consumption, during the six-minute walk test (6MWT) in ten patients with idiopathic PAH. In addition, we sought to determine if there was a relationship between the change in RVSP and the change in gas exchange following several months of therapy with the goal of reducing RVSP. The optimal treatment (medication) was determined by the subjects' doctors and was not recorded for this study. For test 1, we found a negative non-significant relationship between end-tidal carbon dioxide ($P_{ET}CO_2$) and RVSP ($r=-0.6$, $p=0.094$) and a negative non-significant correlation between $P_{ET}CO_2$ and RVSP ($r=-0.7$, $p=0.13$) for test 2. We also found a positive, non-significant correlation between minute ventilation (V_E) relative to carbon dioxide production (V_E/VCO_2) assessed at the mouth and RVSP ($r=0.6$, $p=0.06$) for test 1 and a positive non-significant correlation between V_E/VCO_2 and RVSP ($r=0.5$, $p=0.33$) for test 2. We found a significant drop in RVSP ($p=0.049$), $P_{ET}CO_2$ ($p=0.023$) and V_E/VCO_2 ($p=0.025$) between test 1 and test 2. We found no relationship between the change in RVSP and the change in $P_{ET}CO_2$; we found a moderate, non-significant, relationship between change in RVSP and change in V_E/VCO_2 ($r=0.7$, $p=0.09$). Due to the small sample size there was no significant relationship between the change in RVSP and the change in V_E/VCO_2 ; however, the trend towards significance suggests that the assessment of the gas exchange parameter V_E/VCO_2 may be sensitive enough to determine changes in disease severity in patients with pulmonary hypertension in a study with a larger sample size. In support of this, we performed a post-hoc power analysis and determined that a study with a sample size of 16 would be sufficient to determine changes in RVSP and changes in V_E/VCO_2 . Future studies should look at the relationship between the change of RVSP and the change of V_E/VCO_2 with a larger sample size under standard conditions in regards to treatment and timing between the tests.

Key Words: Pulmonary arterial hypertension, six-minute walk test, echocardiogram

TABLE OF CONTENTS

Acknowledgements.....	i
Abstract.....	ii
Table of Contents.....	iii
List of Tables.....	iv
List of Figures.....	v
Chapter 1. Introduction.....	2
Chapter 2. Review of Literature.....	6
Pulmonary arterial hypertension.....	7
Six-minute walk test.....	8
Echocardiogram.....	10
Chapter 3. Methodology.....	12
Experimental design.....	13
Experiment subjects.....	14
Tests.....	14
Statistical Analysis.....	16
Chapter 4. Results.....	18
Chapter 5. Discussion.....	22
Chapter 6. Conclusion.....	26
References.....	28
Appendix.....	38

LIST OF TABLES

Table 1: Functional classification of disease severity of PAH patients	39
Table 2: Comparison of V_E/V_{CO_2} and $P_{ET}CO_2$ in healthy and PAH subjects.....	40
Table 3: Borg Scale.....	41
Table 4: Demographics of subjects.....	42
Table 5: Six-minute walk test physiology data	43
Table 6: Differences of gas exchange and RVSP for test 1 and 2.....	44
Table 7: Correlations of $P_{ET}CO_2$, V_E/V_{CO_2} , RVSP between test 1 and 2.....	45
Table 8: Change between $P_{ET}CO_2$, V_E/V_{CO_2} and RVSP for test 1 and 2.....	46

LIST OF FIGURES

- Figure 1: Correlation between RVSP and V_E/V_{CO_2} for test 1 ($r=0.6$, $p=0.06$)...47
- Figure 2: Correlation between RVSP and V_E/V_{CO_2} for test 2 ($r=0.5$, $p=0.33$)...48
- Figure 3: Correlation between RVSP and $P_{ET}CO_2$ for test 1 ($r=0.6$, $p=0.06$)....49
- Figure 4: Correlation between RVSP and $P_{ET}CO_2$ for test 2 ($r=0.7$, $p=0.13$)....50

CHAPTER 1. INTRODUCTION

Pulmonary Arterial Hypertension (PAH) is an uncommon disease that affects the blood flow through the lungs. There are 7.1 PAH cases per million of which 46% are diagnosed with idiopathic PAH (Peacock, 2007). Although the disease is rare, PAH has increasingly become a focus of research studies given the poor prognostic outcomes in patients with PAH and the fact that early diagnosis can result in a marked improvement in quality of life. PAH can affect any gender, ethnicity, and age, although it is more commonly reported in adulthood (Lung Foundation, 2011). Chronic obstruction of the blood vessels in the lungs raises the blood pressure of the pulmonary arteries over time, which results in an increased workload for the heart.

The Lung Foundation lists several types and causes of PAH (Lung Foundation, 2011) which include:

- Primary pulmonary hypertension (familial and idiopathic)
- Scleroderma (also known as systemic sclerosis)
- Lupus
- HIV/AIDS
- Congenital heart defects
- Some liver disorders
- Certain drugs or toxins

Depending on the severity of the disease the impact of PAH on daily life can range from little (Class I) where the patient has no limitation in daily or physical

activity to severe (Class IV) where the patient encounters breathlessness, fatigue and dizziness at a rested state (Table 1).

Because the symptoms of PAH can be mistaken for other diseases, several tests are required to diagnose the patient with PAH. The Lung Foundation suggests echocardiograms, breathing and walking tests, computed tomography (CT) scans and a right heart catheterization to correctly diagnose PAH (Lung Foundation, 2011). The gold standard for the assessment of pulmonary artery pressure is right heart catheterization, but this procedure is invasive, expensive and requires a highly-specialized team to perform the procedure. The disease severity of PAH is best diagnosed non-invasively through assessment of RVSP via echocardiogram since the main cause of PAH is obstruction of the pulmonary blood vessels which can be assessed as a back-pressure on the right side of the heart. (Howard, 2011; Pietra, 1989) However, echocardiography remains somewhat expensive, requires the skills of an ultrasound technician, and may require the use of a contrast agent to assess RVSP due to low signal strength of the variable used to assess RVSP, tricuspid regurgitant velocity (TRV). Based on the limitations of right heart catheterization and echocardiography, a non-invasive test for PAH is needed. The six minute walk test (6MWT) would be a less expensive and easier tool to assess disease status.

The 6MWT is a well-established test for pulmonary function, especially in patients with cardiopulmonary disease, as it does not require a maximal effort (Rasekaba and Lee et al. 2009; Paciocco, 2001). However, there is some evidence to suggest that the 6MWT is not sensitive to disease severity, particularly in younger individuals more likely to reach a 6MWT ceiling (Rasekaba and Lee et al., 2009). Recent evidence suggests that the gas exchange measurements made during exercise in PAH patients are unique to PAH and may reflect disease severity (Hansen, 2007). For this pilot study, a repeated measures study design was utilized in which we sought to examine the relationship between gas exchange measurements made during the 6MWT and disease severity in patients with PAH and to determine if gas exchange measurements during 6MWT were sensitive enough to determine changes in disease severity.

CHAPTER 2. REVIEW OF LITERATURE

Pulmonary arterial hypertension

PAH is defined as a sustained elevation of pulmonary arterial pressure of >25 mmHg at rest and >30 mmHg with exercise (Table 2) (Tolle, 2008). Pathogenic factors resulting in PAH include scarring of connective tissue (fibrosis), blood clot (thrombosis), enlargement of the walls (myocardial ventricular hypertrophy), and constriction of the pulmonary arterial blood vessels (vasoconstriction) (Smith, 2013) which result in a decreased intraluminal diameter and an increased pulmonary vascular resistance (Smith, 2013). The increase in vascular resistance raises the pulmonary arterial pressure resulting in PAH (Gaine, 1998). The remodeling of the pulmonary arterial walls due to sclerosis and fibrosis impairs the oxygen diffusion from the lungs into the blood stream (Smith, 2013) and from carbon dioxide (CO_2) from the blood out of the lungs. This ventilation-perfusion mismatch results in an increased dead space, a decreased partial pressure of end-tidal carbon dioxide (P_{ETCO_2}), and an increased ventilatory requirement (Sun, 2001). In PAH patients, P_{ETCO_2} is even further attenuated with exercise (Riley, 2000). The increased ventilation requirement is shown as an elevated ventilatory equivalent ratio for CO_2 (V_E/V_{CO_2}) ratio. From a disease standpoint P_{ETCO_2} is lower in patients with pulmonary hypertension, because there is an inability for CO_2 to diffuse from the blood through the lungs (Yasunobu, 2005; Hansen, 2014). Lower P_{ETCO_2} and higher V_E/V_{CO_2} are indicative of more severe pulmonary hypertension. V_E/V_{CO_2} in resting and exercising states falls below 30 in healthy subjects (Arena, 2009) indicating that

the CO_2 production and V_E increase at the same rate. However, in PAH patients, the ratio is between 30 to 60 due to increased ventilation with decreased exhalation of CO_2 . $P_{\text{ET}}\text{CO}_2$ in healthy subjects ranges between high 30s to low 40s mmHg at rest with an increase of 3 - 8 mmHg during exercise (Arena, 2009). In PAH patients resting values of $P_{\text{ET}}\text{CO}_2$ fall between low 20s to low 30s mmHg and during exercise ranges from low 30s down to 18 mmHg (Table 2). With increased disease severity the change of resting to exercising $P_{\text{ET}}\text{CO}_2$ decreases whereas in healthy subjects it increases (Arena, 2009). Historically, the function of the right ventricle is essential to determine the severity and disease status of the pulmonary disease (Voelkel, 2006). The RVSP is typically evaluated using invasive (right heart catheterization) or expensive (such echocardiography or magnetic resonance imaging) techniques. Several non-invasive tests have been used to evaluate the severity of PAH; the most accessible is the well-established 6MWT. This test has sound clinical guidelines (ARHP Research Committee, 2011), requires little equipment, and is self-regulating by the patient and, as such, does not require high-intensity efforts which could be potentially harmful.

Functional testing of PAH

Six-minute walk test

The 6MWT is a test designed for patients with heart failure or chronic respiratory diseases to measure functional exercise capacity (ARHP Research Committee, 2011). The purpose of the test is to cover as much distance as possible in six

minutes. The walking course is 30 meters and is marked by cones or tape which the subject walks between. Exercise testing like the 6MWT provides a valid assessment of heart function since distance covered is correlated to the oxygen uptake (VO_2) (Deboeck and Niset et al., 2005; ARHP Research Committee, 2011) and there is a direct relationship between maximal cardiac output and oxygen delivery and consumption (Howard, 2011). Thus, the 6MWT is a safe, easy, and non-invasive measurement of functional capacity. One previous study (Deboeck and Niset et al., 2005) compared the maximal oxygen uptake (VO_{2max}) of PAH patients of the 6MWT with the gas exchange parameters during a cardiopulmonary bicycle exercise test. In this study the VO_{2max} for the 6MWT was higher than the bicycle test. Deboeck suggested that one of the reasons could be that PAH patients do not have the required lower body muscle mass to achieve maximum cardiac output so whole-body exercise may be more accurate. The protocol of the 6MWT matches with the typical exercise pattern for PAH patients and is therefore a more accurate tool for PAH patients to obtain VO_{2max} than the bicycle exercise test. Even the simple assessment of distance walked during a 6MWT could be a powerful tool for patients with PAH in hospitals and centers that lack a portable VO_2 testing device. A comparison study by Oudiz and Barst et al. (2006) showed a high correlation between VO_2 and walking distance if the test is conducted by trained staff and the results are weight-adjusted (Oudiz , 2006). Since the walk test can vary due to perceptual variations, Redelmaier et al. suggests a distance difference of 54 meters

between tests to be clinical significant (Redelmeier and Bayoumi et al., 1997). The average distance for the 6MWT in PAH patients is 297 m (Rasekaba and Lee et al., 2009). Although the distance walked is important, it is likely that the assessment of gas exchange parameters gives the clinician more information regarding disease severity. In addition to measures of gas exchange, the assessment of oxygen saturation ($O_2 \text{ sat}$) during exercise is important in patients with PAH. $O_2 \text{ sat}$ is a relative measure of the amount of oxygen that the blood can carry expressed as a percent of hemoglobin saturated with oxygen. Patients with more severe pulmonary hypertension can demonstrate drops in arterial $O_2 \text{ sat}$ due to ventilation-perfusion mismatching. A study by Paciocco et al. researched the relationship between distance walked of the 6MWT and oxygen desaturation and found that a change of $O_2 \text{ sat}$ between rest time and peak time of >10% increased mortality by 2.9 years (Paciocco, 2001).

Echocardiogram

The echocardiogram uses ultrasound waves to assess the structure and function of the heart. Since PAH is defined as an elevated pulmonary arterial pressure (PAP), the echocardiogram is a useful but rather expensive tool to diagnose PAH (Mathai, 2008). The echocardiogram allows measuring the RSVP through the assessment of TRV which assesses back pressure from the lungs. The TRV is derived through the Doppler evaluation and the PAP is calculated $4 \cdot \text{TRV}^2 + 5$ mmHg (Chan, 1987), where 5 mmHg is an estimate of right atrial pressure.

RSVP in healthy subjects is below 25 mmHg; however, due to increased arterial stenosis, RSVP in PAH patients increases to over 25 mmHg.

The purpose of this pilot study was to determine if there was a relationship between RVSP (measured by an echocardiogram) and gas exchange (measured during a 6MWT). We focused on RVSP, $P_{ET}CO_2$ and V_E/VCO_2 as these are indicators for disease severity.

CHAPTER 3. METHODOLOGY

Experimental Design

To determine the relationship between gas exchange and RVSP in patients with PAH, we assessed both variables before (test 1) and following (test 2) treatment guided to reduce RVSP. First, we looked at the relationship between our three main variables (RVSP, $P_{ET}CO_2$, V_E/VCO_2) within each test. Then we compared the change between test 1 and test 2 within each variable. Finally, we correlated the change between test 1 and test 2 of the gas exchange variables to the change between test 1 and test 2 to RVSP. If there is a relationship between the changes of disease severity and the changes of gas exchange, the 6MWT can become a more-widely used tool, possibly in place of the more expensive echocardiogram as a measurement of the change in disease status following treatment in patients with PAH in order to further guide therapy.

Experimental subjects

Ten subjects identified with idiopathic PAH were recruited for this study from the Prince Charles hospital (Brisbane, Australia). All subjects were patients at Prince Charles hospital, had idiopathic PAH, and gave written consent for participation of this study. Subjects were excluded from the study if they were not able to walk, claustrophobic, or on a permanent oxygen delivery device. To compare the PAH values to a healthy range we used the values indicated by a pulmonary hypertension review by Arena (2009). The subject was informed about the test and signed the consent form for the study. The subjects were recruited due to the idiopathic nature of their disease. The two tests were part of the standard testing for the subjects and were separated by several months of treatment with the goal of reducing RVSP. Treatments were not recorded and thus were not part of the analysis of this study. Since the purpose of this pilot study was to determine if there is a relationship between two assessment tools for the severity of PAH, it did not include any other variables but two tests with their respective measurements of RVSP, $P_{ET}CO_2$ and V_E/VCO_2 .

Six-minute walk test

Every subject performed two tests (6MWT and echocardiogram as described below) on two different days that were separated by at least one month. These tests were part of the regular check-up routine. The average time between the 6MWTs was one year and four months. Both testing days were

identical, other than the subjects were treated with the goal of reducing RVSP prior to the post-therapy test (test 2). To determine gas exchange, the trained medical staff placed a face mask over the mouth of the sitting subject and put the portable metabolic analyzer, which was calibrated before each test (Cortex, MetaMax, Koln, Germany). The portable metabolic analyzer fitted like a vest around the subject and was loosely tightened to ensure it would not fall off while walking. To measure O_2 Sat, two electrodes of the pulse oximeter were placed above each eye brow and secured with a headband. The pulse oximeter device (Nonin Medical, Inc., Plymouth, Minnesota, MN, USA) was held by the physiotherapist during the test. A heart rate strap (Polar, Kempele, Finland) was tightened below the chest of the subject. The staff instructed the subject about the Borg scale (Table 3), which was used during the 6MWT. The Borg scale is a scale that ranges from 6 to 20 with 6 being resting with no physical exertion and 20 being maximal exercise. When the subject was ready, the physiotherapist and the subject advanced to the start line of the walk test. Once the subject was ready, the physiotherapist started the clock and the subject walked as fast as his or her ability allowed between the marked 30 m distance in the hallway. The physiotherapist walked slightly behind the subject to ensure that the subject went his or her own pace. Every minute, the physiotherapist asked the subject for his or her rate of perceived exertion on the aforementioned scale. During the walk, another staff member recorded all completed laps and noted heart rate, O_2 Sat and the Borg scale number every full minute. A third staff member monitored the

data on a laptop that received all live data about the subject. At minute six, the subject stopped. Any incomplete lap was not recorded. The subject was then brought to a chair and the tube of the facemask was removed so the subject was able to breathe freely. Heart rate and O_2 sat were monitored and recorded until it dropped to pre-exercise values. Following the return to pre-exercise values the heart rate strap, pulse oximeter and metabolic vest were removed by the staff. Each subject also underwent two echocardiograms (Vingmed Vivid-7® echocardiograph, analysis using EchoPAC) which were conducted in the same time frame as their respective 6MWTs. The time frame ranged from six months to two years between tests. For the purpose of this study, only the RVSP was recorded. During the echo, the patient removed clothes to expose the chest. The subject was connected to an EKG monitor to record the electrical activity of the heart. The cardiologist applied gel to the patient's chest and positioned the transducer on the chest to receive an image of the heart. During the test, the cardiologist repositioned the transducer to image different angles from the heart to optimize the signal from the heart chambers. After the test, the doctor wiped down the gel from the chest and removed the EKG electrode pads. The patient dressed again.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 19 software (SPSS, Chicago, IL, USA). Descriptive statistics included demographic variables

(age, height, weight) (Table 3) and gas exchange variables (V_E , oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), heart rate (HR), partial pressure for end-tidal oxygen tension ($P_{ET}O_2$), $P_{ET}CO_2$, O_2 Sat, V_E/VCO_2 , 6MWT) (Table 4). We used a Pearson's correlation to determine the relationship between baseline RVSP and $P_{ET}CO_2$, and V_E/VCO_2 . We also used a repeated-measures t-test to assess the change in RVSP, $P_{ET}CO_2$ and V_E/VCO_2 between test 1 and test 2 (Table 6). In addition, we assessed the relationship between the change in RVSP and change in gas exchange parameters. An alpha level of 0.05 was used to determine statistical significance. Finally, we used G*Power software for a post-hoc power analysis to determine the sample size needed to reach significance between the change of V_E/VCO_2 and the change of RVSP.

CHAPTER 4. RESULTS

Characteristics of the patients

Table 3 contains the demographic characteristics of all subjects. The mean age of the subjects was 47 ± 13 years. The height of the subjects ranged from 155 cm to 190 cm with a mean of 168 cm. The mean weight of the subjects was 73 ± 20 kg. The body mass index (BMI) ranged from 19 to 36 kg/m^2 with a mean of 25 kg/m^2 .

Six-minute walk test physiology data

Table 5 describes the physiological values of the 6MWT. The mean distance for the first 6MWT was 557 ± 86 m. For the second 6MWT, the mean distance was 550 ± 126 m. Before test 1, $\text{O}_2 \text{ sat}$ had a mean of 98 ± 4 percent while the mean before the second 6MWT was 98 ± 1.5 percent. The lowest mean $\text{O}_2 \text{ sat}$ for test 1 was 94 ± 4 percent and 94 ± 4.5 percent for test 2. The heart rate before the first 6MWT averaged 76 ± 8 beats/min and 77 ± 14 beats/min for test 2. There was a significant difference between the maximum heart rate of test 1 (170 ± 8 beats/min) and test 2 (137 ± 25 beats/min) ($p=0.04$). There was a significant change of VCO_2 post-6MWT from test 1 ($0.4 \pm 0.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to test 2 ($0.95 \pm 0.24 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) ($p=0.03$). There was no significant change of VO_2 post-6MWT between test 1 ($1 \pm 0.4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and test 2 ($0.9 \pm 0.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). V_E after the 6MWT was 53 ± 21 l/min and 39 ± 14 l/min for test 1 and test 2, respectively. The respiratory exchange ratio (RER) was 1.0 ± 0.4 (test 1) and 1.0 ± 0.2 (test

2). The $P_{ET}O_2$ was 116 ± 7 mmHg and 120.7 ± 8 mmHg for test 1 and test 2, respectively. $P_{ET}CO_2$ was 28 ± 6 mmHg (test 1) and 29 ± 7 mmHg (test 2).

Differences of $P_{ET}CO_2$, V_E/VCO_2 , RVSP between test 1 and test 2

Table 6 shows the results of the paired-samples t-tests within $P_{ET}CO_2$, V_E/VCO_2 and RVSP for test 1 and 2. The change between $P_{ET}CO_2$ test 1 and test 2 was significant ($p=0.03$), a decrease from a mean of 29 ± 7 mmHg to a mean of 26 ± 6 mmHg. The difference between test 1 and test 2 of V_E/VCO_2 was significant ($p<0.05$) as it increased from 39 ± 9 mmHg to 44 ± 10 mmHg. There was also a significant difference between test 1 and test 2 for RVSP ($p=0.023$). For test 1, the mean of RVSP was 67 ± 21 mmHg and decreased to 59 ± 16 mmHg for test 2.

Correlations of $P_{ET}CO_2$, V_E/VCO_2 , RVSP between test 1 and 2

As shown in Table 7, within each test, there was no significant relationship between the variables. There was a positive non-significant correlation ($r=0.6$, $p=0.06$) (Figure 1) between RVSP and V_E/VCO_2 in test 1 and a positive non-significant correlation ($r=0.5$, $p=0.33$) (Figure 2) between RVSP and V_E/VCO_2 in test 2. We found a non-significant negative relationship between $P_{ET}CO_2$ and RVSP ($r=-0.6$, $p=0.094$) (Figure 3) in test 1 and a negative correlation between $P_{ET}CO_2$ and RVSP ($r=-0.7$, $p=0.13$) (Figure 4) in test 2.

Relationship between changes in RVSP and changes in gas exchange

Table 8 demonstrates the relationships between the changes of RVSP and the changes of gas exchange. The changes of RVSP and the changes of $P_{ET}CO_2$ were not correlated and had no significance ($r=0.2$, $p=0.69$). The changes between RVSP and V_E/VCO_2 were non-significantly related ($r=0.7$, $p=0.09$).

CHAPTER 5. DISCUSSION

The mean of $P_{ET}CO_2$ was 29 mmHg for test 1 and 25 mmHg for test 2 which shows the impact of PAH on $P_{ET}CO_2$. The decreasing $P_{ET}CO_2$ value between test 1 and test 2, similar to a study by Dumitrescu et al. (2012) suggests a decline of pulmonary function. The $P_{ET}CO_2$ value of a healthy person ranges from 30 - 40 mmHg. In our study, $P_{ET}CO_2$ further decreases during exercise while in healthy subjects $P_{ET}CO_2$ increases. This opposing trend of $P_{ET}CO_2$ in PAH patients demonstrates why their capacity for exercise may be limited.

The mean of the V_E/VCO_2 slope of 39 and 44 (for test 1 and test 2, respectively) compared to the previously-published healthy range (Arena, 2009) of below 30 shows the impact of PAH on V_E/VCO_2 . This suggests that PAH patients have a lower output of CO_2 despite increased ventilation. Since PAH patients suffer from the obstruction of blood vessels that impairs the blood flow in the lungs, their pulmonary gas exchange is drastically inhibited. Moreover, when exposed to exercise, the V_E/VCO_2 is further increased which suggests that the increased blood flow worsens the gas exchange in the lungs. Despite worsening of the ventilatory efficiency, RVSP decreased from 67 mmHg to 59 mmHg from test 1 to test 2. The decreased RVSP could be traced back to medication that the PAH patients received between the two tests, although the exact medications that each subject used was beyond the scope of this pilot study. The common medication for PAH, Isordil, is a vasodilator and thus decreases the blood pressure. However, as the values indicate, despite decreasing RVSP, the gas

exchange ($P_{ET}CO_2$) has not improved. This opposing trend between gas exchange (worsens) and RVSP (improves) suggests a non-reversible, physiological change of the pulmonary arteries and indicates that gas exchange might be a more accurate measurement of disease severity than RVSP in an advanced state of PAH. Within each test, we did not find any relationship between gas exchange and RVSP; however, RVSP, V_E/VCO_2 and $P_{ET}CO_2$ are significantly correlated when comparing each variable between the two tests. Moreover, when we correlated the changes of each variable to each other (Table 8) we found a trend towards a significant relationship between the change of RVSP and the change of V_E/VCO_2 ($p=0.09$). These results suggest that V_E/VCO_2 could be a good predictor for assessing disease severity without the need for an echocardiogram, however, this pilot data needs to be confirmed with a larger sample size.

Limitations

As this was a pilot study, we had a relatively small group of subjects with trends in several parameters which suggests that this study was not powered to detect differences in some variables that have a small effect size. Although we found a non-significant relationship between the changes of V_E/VCO_2 measured using 6MWT and the change of RVSP ($p=0.09$) measured using echocardiography we calculated that there would likely be statistical significance ($p=0.05$) with an increased sample size ($n= 16$) calculated with power analysis (G*Power,

Duesseldorf, Germany). In addition, we compared the 6MWD with the echocardiogram; however, the gold standard for assessing pulmonary hypertension is cardiac catheterization. Due to the invasive nature of cardiac catheterization, we used the echocardiogram to assess the validity of the 6MWD. A study by Arcasoy et al. found an overestimation of disease severity in PAH patients using an echocardiogram because of several reasons. First, the measurement of TRV tends to be inaccurate some patients (Litwin, 2010). The amount of the regurgitant volume must be great enough to be useful to measure TRV. Even with an appropriate amount of blood volume, TRV is derived through an estimation of PAP (Litwin, 2010) which can cause errors. However, generally speaking, a study by Attaran (2009) found a strong correlation (0.49; $P < .001$) of PAP estimated by echo versus right heart catheterization. Furthermore, although the 6MWT is a widely used submaximal testing tool, it could be replaced with other submaximal tests that could be easier to conduct and standardize. A study by Noonan et al. (2000) implemented a different submaximal exercising protocol and concluded that other submaximal tests might be more sensitive, valid and reliable than the 6MWT (for instance, exercise tests on a treadmill could be more standardized). In addition, Future studies should look at 6MWD compared to right heart catheterization and gas exchange measurements utilizing a larger sample size under standard conditions in regards to treatment and timing between the tests.

CHAPTER 6. CONCLUSION

The purpose of the present pilot study was to determine whether the values of the 6MWD ($P_{ET}CO_2$ and V_E/VCO_2) can be correlated to the values of the echocardiogram (RVSP) and thus the 6MWT could be utilized as an additional tool in patients with PAH, or (as necessary) possible replace the more expensive echocardiogram in some clinics. Our study showed that V_E/VCO_2 may be a good predictor for disease severity as it was closely related to the RVSP – an essential determinant for the longevity of PAH – however, our results did not reach statistical significance because we were underpowered (Voelkel, 2006).

REFERENCES

- Arena, Ross, and Carl J. Lavie. "Cardiopulmonary Stress Testing in Patients With Pulmonary Artery Hypertension." *Mayo Clinic Proceedings* 84.10 (2009): 939. Print.
- Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med*. 2003;167:735-740.
- ARHP Research Committee, 2011, Six Minute Walk Test, American College of Rheumatology, [http://www.rheumatology.org/Practice/Clinical/Clinicianresearchers/Outcomes_Instrumentation/Six_Minute_Walk_Test_\(6MWT\)](http://www.rheumatology.org/Practice/Clinical/Clinicianresearchers/Outcomes_Instrumentation/Six_Minute_Walk_Test_(6MWT)).
- Attaran R.R, R. Ramaraj, V.L. Sorrell, and M.R. Movahed, Poor Correlation of Estimated Pulmonary Artery Systolic Pressure Between Echocardiography and Right Heart Catheterization in Patients Awaiting Cardiac Transplantation: Results From the Clinical Arena, Transplantation Proceedings, 2009-11-01, Volume 41, Issue 9, Pages 3827-3830
- Barst R, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12s1):S40-S47. doi:10.1016/j.jacc.2004.02.032.
- Benza Raymond L., Dave P. Miller, et al. Predicting Survival in Pulmonary Arterial Hypertension: Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial, Hypertension Disease Management (REVEAL), *Circulation*. 2010;122:164-172, published online before print June 28 2010, oi:10.1161/CIRCULATIONAHA.109.898122
- Chan K.L, Currie P.J, Seward J.B, Hagler D.J, Mair D.D, Tajik J; Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery disease. *J Am Coll Cardiol*. 9 1987:549-554.
- Deboeck, G., Niset, G., Vachiery, J., Moraine, J. and Naeije, R. 2005. Physiological response to the six-minute walk test in pulmonary arterial hypertension. *European Respiratory Journal*, 26 (4), pp. 667--672.
- Denton CP, J B Cailles, G D Phillips, A U Wells, C M Black, and R M Bois Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Rheumatology* (1997) 36 (2): 239-243 doi:10.1093/rheumatology/36.2.239
- Dumitrescu, D.. "Gas exchange measurements during exercise show early pulmonary arterial hypertension in scleroderma patients." *European*

Heart Journal; 33 (2012): 46. Print.

Gaine, Sean P, and Lewis J Rubin. "Primary pulmonary hypertension." The Lancet 352.9129 (1998): 719-725. Print.

Galiè E, N., Hoeper, M. M., Humbert, M., Torbicki, A., Vachiery, J., Barbera, J. A., Beghetti, M., Corris, P., Gaine, S., Gibbs, J. S. and Others. 2009. Guidelines for the diagnosis and treatment of pulmonary hypertension The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). European heart journal, 30 (20), pp. 2493--2537.

Hansen, James. "Mixed-Expired and End-Tidal CO2 Distinguish Between Ventilation and Perfusion ." Chest 132.3 (2007): 977-983. Chest. Web. 19 Apr. 2014.

Howard, L. 2011. Prognostic factors in pulmonary arterial hypertension: assessing the course of the disease. European Respiratory Review, 20 (122), pp. 236--242.

Sheldon E. Litwin, Noninvasive Assessment of Pulmonary Artery Pressures: Moving Beyond Tricuspid Regurgitation Velocities Circ Cardiovasc Imaging. 2010;3:132-133, doi:10.1161/CIRCIMAGING.110.945121

Lung Foundation, Pulmonary Arterial Hypertension, 2005, <http://www.lungfoundation.com.au/lung-information/interstitial-and-orphan-lung-diseases/pulmonary-arterial-hypertension-2/>

Mathai, Stephen . "The Role of Echocardiography in the Diagnosis and Assessment of Pulmonary Hypertension." Advances in pulmonary Hypertension 7.4 (2008): n. pag. Advances in PH Journal. Web. 19 Apr. 2014.

Mathier, Mathias. "The Classification of Pulmonary Arterial Hypertension." Medscape Education Pulmonary Medicine 1 (2006): The Classification of Pulmonary Arterial Hypertension. Web. 3 May 2014.

McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis Of Pulmonary Arterial Hypertension*: Accp Evidence-Based Clinical Practice Guidelines Chest. 2004;126(1_suppl):78S-92S.

Miyamoto Shoichi, Noritoshi Nagaya et al. Clinical Correlates and \

Prognostic Significance of Six-minute Walk Test in Patients with Primary Pulmonary Hypertension. *American Journal of Respiratory and Critical Care Medicine* 2000 161:2, 487-492.

<http://www.atsjournals.org/doi/abs/10.1164/ajrccm.161.2.9906015#.U15doPmSzNI>

Mukerjee D, D. St. George, C. Knight, J. Davar, A. U. Wells, R. M. Du Bois, C. M. Black, and J. G. Coghlan

Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis

Rheumatology (2004) 43 (4): 461-466 first published online January 6, 2004 doi:10.1093/rheumatology/keh067

Noonan, Vanessa, Elizabeth Dean; Submaximal Exercise Testing: Clinical Application and Interpretation *PHYS THER* August 2000 80:782-807

Norbert F. Voelkel, Robert A. Quaife, Leslie A. Leinwand, Robyn J. Barst, Michael D. McGoon, Daniel R. Meldrum, Jocelyn Dupuis, Carlin S. Long, Lewis J. Rubin, Frank W. Smart, Yuichiro, J. Suzuki, Mark Gladwin, Elizabeth M. Denholm, and Dorothy B. Gail Right Ventricular Function and Failure: Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure, *Circulation*. 2006;114:1883-1891, doi:10.1161/CIRCULATIONAHA.106.632208

Oudiz, R. J., Barst, R. J., Hansen, J. E., Sun, X., Garofano, R., Wu, X. and Wasserman, K. 2006. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. *The American journal of cardiology*, 97 (1), pp. 123--126.

Oudiz, R, G Roveran, J Hansen, X Sun, and K Wasserman. "Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension ☆." *European Journal of Heart Failure* 9.9 (2007): 917-921. Print.

Paciocco, G., F.j. Martinez, E. Bossone, E. Pielsticker, B. Gillespie, and M. Rubenfire. "Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension." *European Respiratory Journal* 17.4 (2001): 647-652. Print.

Peacock A.J., N. F. Murphy, J. J. V. McMurray, L. Caballero, and S. Stewart An epidemiological study of pulmonary arterial hypertension *Eur Respir J* 2007 30:104-109; published ahead of print 2007, doi:10.1183/09031936.00092306

Pietra, G. G., B. H. Brundage, E. H. Bergofsky, S. M. Ayres, B. Schloo, J. Kernis, S. Rich, J. M. Kay, W. D. Edwards, and K. M. Detre. "Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry." *Circulation* 80.5 (1989): 1198-1206. Print.

Rasekaba, T., Lee, A., Naughton, M., Williams, T. and Holl. 2009. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Internal medicine journal*, 39 (8), pp. 495--501.

Redelmeier, D. A., Bayoumi, A. M., Goldstein, R. S. and Guyatt, G. H. 1997. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. *American journal of respiratory and critical care medicine*, 155 (4), pp. 1278--1282.

Gas exchange responses to continuous incremental cycle ergometry exercise in primary pulmonary hypertension in humans

Riley, Marshall S. ; Pórszász, János ; Engelen, Mariëlle P. K. J. ; Brundage, Bruce H. ; Wasserman, Karlman *European Journal of Applied Physiology*, 2000, Vol.83(1), pp.63-70 [Peer Reviewed Journal]

Sawada Stephen G., Thomas Ryan, Mary Jo Conley, Betty C. Corya, Harvey Feigenbaum, William F. Armstrong, Prognostic value of a normal exercise echocardiogram, *American Heart Journal*, Volume 120, Issue 1, July 1990, Pages 49-55, ISSN 0002-8703, [http://dx.doi.org/10.1016/0002-8703\(90\)90159-U](http://dx.doi.org/10.1016/0002-8703(90)90159-U).
(<http://www.sciencedirect.com/science/article/pii/000287039090159U>)

Simonneau G, Robbins IM, Beghetti M, et al. Updated Clinical Classification of Pulmonary Hypertension. *J Am Coll Cardiol*. 2009;54(1s1):S43-S54. doi:10.1016/j.jacc.2009.04.012.

Smith, JS. "Pulmonary hypertension and idiopathic pulmonary fibrosis: a dastardly duo." *American Journal of Medical Science* 346 (2013): 221-5. Print.

Sun, XG, Hansen, JE, Oudiz, RJ, et al Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001;104,429-435.

Tolle James J., Waxman Aaron B., Teresa L. Van Horn, Paul P. Pappagianopoulos, and David M. Systrom, Exercise-Induced Pulmonary

Arterial Hypertension, *Circulation*. 2008;118:2183-2189, published online before print November 3 2008,
doi:10.1161/CIRCULATIONAHA.108.787101

van Wolferen Serge A., Johannes T. Marcus, Anco Boonstra, Koen M.J. Marques, Jean G.F. Bronzwaer, Marieke D. Spreeuwenberg, Pieter E. Postmus, and Anton Vonk-Noordegraaf
Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension
Eur Heart J (2007) 28 (10): 1250-1257 first published online January 22, 2007 doi:10.1093/eurheartj/ehl477

Yasunobu, Y.. "End-tidal PCO2 Abnormality and Exercise Limitation in Patients With Primary Pulmonary Hypertension." *Chest* 127.5 (2005): 1637-1646. Print.

Yock P G and R L Popp. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation*. 1984;70:657-62, doi:10.1161/01.CIR.70.4.657
<http://circ.ahajournals.org/content/70/4/657.short>

APPENDIX

Table 1: Functional classification of disease severity of PAH patients (Simonneau, 2009)

A. New York Heart Association functional classification	
Class 1:	No symptoms with ordinary physical activity.
Class 2:	Symptoms with ordinary activity. Slight limitation of activity.
Class 3:	Symptoms with less than ordinary activity. Marked limitation of activity.
Class 4:	Symptoms with any activity or even at rest.
B. World Health Organization functional assessment classification	
Class I:	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III:	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.
Table reprinted with permission from Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Introduction. Chest. 2004; 126:7S-10S.	

Table 2: Comparison of V_E/V_{CO_2} and $P_{ET}CO_2$ in healthy and PAH subjects (Arena, 2009)

		Healthy	PAH
V_E/V_{CO_2}	Rest	<30s	30s-60s
	Post-exercise	<30s	30s-60s
$P_{ET}CO_2$ (mmHg)	Rest	High 30s-low 40s	low 20s-low 30s
	Post-exercise	3-8 mmHg increase	low 30s – 18
<p>$P_{ET}CO_2$- partial pressure of end-tidal carbon dioxide 2 - V_E/V_{CO_2}-Ventilatory equivalent ratio for carbon dioxide</p> <p>* In healthy subjects $P_{ET}CO_2$ increases with exercise. However, in PAH patients it flattens or even decreases which is conversely related to disease severity.</p>			

Table 3: Borg Scale

6	No exertion
7	
8	
9	
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	
20	Maximal exertion

Source: <http://www.vavaveteran.co.uk/wp-content/uploads/2013/04/RPE.jpg>

Table 4: Demographics of subjects

	Mean		SD	Range
Age (years)	47.89	±	12.7	26 - 66
Height (cm)	168.88	±	11.6	155 - 190
Weight (kg)	72.75	±	20.2	48 - 109
Body Mass Index (BMI) (kg/m ²)	25.22	±	5.18	18.7 - 35.6

Table 5: Six-minute walk test physiology data

	N	Test1	Test 2	Difference	p
6MWD (m)	10	557 ± 86	550 ± 126	-57	0.89
O ₂ Sat pre* ¹ (%)	10	98 +4	98 ± 1.5	0	1
O ₂ Sat min (%)	10	94 ± 4	94 ± 4.5	0	1
HR pre (beats/min)	10	76 ± 8	77 ± 14	1	0.89
HR max (beats/min)	10	170 ± 8	137 ± 25	-33	0.04*
VO ₂ post* ² (mL . kg ⁻¹ . min ⁻¹)	8	1 ± 0.4	0.9 ± 0.3	-0.1	0.66
VCO ₂ post (mL . kg ⁻¹ . min ⁻¹)	8	0.4 ± 0.1	0.9 ± 0.24	0.55	0.03*
V _E post (l/min)	8	53 ± 21	39 ± 14	-14	0.26
RER	8	1 ± 0.4	1 ± 0.2	0	1
P _{ET} O ₂ (mmHg)	8	116 ± 7	121 ± 8	4	0.13
P _{ET} CO ₂ (mmHg)	8	29 ± 7	26 ± 6	-3	0.03*

HR- heart rate 6MWD- Distance walked during 6-minute walk test

O₂ Sat- saturation level of oxygen in hemoglobin

RER-respiratory exchange ratio, VO₂ – oxygen consumption rate, VCO₂ – carbon dioxide consumption rate, V_E- minute ventilation, P_{ET}O₂- partial pressure of expiratory oxygen, P_{ET}CO₂ – partial pressure of end-tidal CO₂, *1 pre- before test, *2 post-test, * significant

Table 6: Differences of gas exchange and RVSP for test 1 and 2

	Test 1	Test 2	p
$P_{ET}CO_2$ (mmHg)	29 ± 7	26 ± 6	0.03*
RVSP (mmHg)	67 ± 21	59 ± 16	0.02*
V_E/VCO_2 slope	39 ± 9	44 ± 10	0.05*

V_E/VCO_2 -Ventilatory equivalent ratio for carbon dioxide

RVSP-Right ventricular systolic pressure

$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide

* 0.05 significant

Table 7: Correlations of $P_{ET}CO_2$, V_E/VCO_2 , RVSP between test 1 and 2

	RVSP (mmHg)			
	Test 1		Test 2	
	p	r	p	r
$P_{ET}CO_2$ (mmHg)	0.094	-0.557	0.13	-0.689
V_E/VCO_2 slope	0.06	0.612	0.33	0.485

$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide

V_E/VCO_2 -Ventilatory equivalent ratio for carbon dioxide

RVSP-Right ventricular systolic pressure

* 0.05 significant

Table 8: Change between $P_{ET}CO_2$, V_E/VCO_2 and RVSP for test 1 and 2

	RVSP (mmHg)	
	Δ Test 1-2	
	p	r
$P_{ET}CO_2$ (mmHg)	0.699	0.18
V_E/VCO_2 slope	0.09	0.69

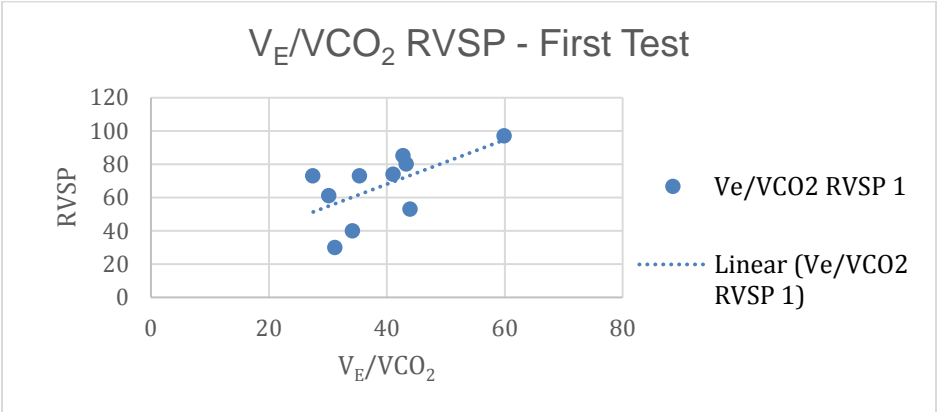
V_E/VCO_2 -Ventilatory equivalent ratio for carbon dioxide

RVSP-Right ventricular systolic pressure

$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide

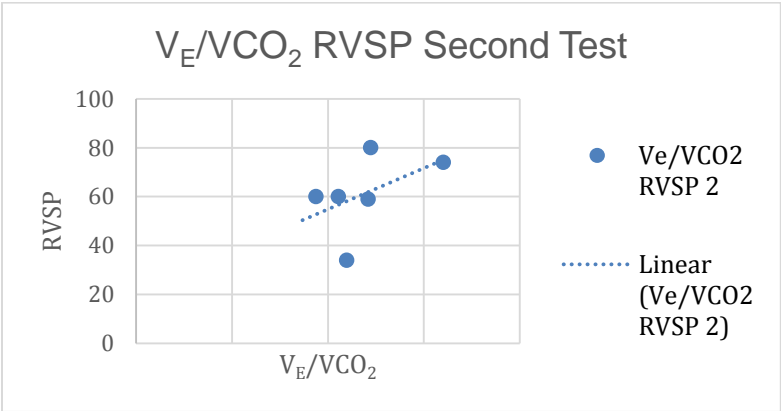
* 0.05 significant

Figure 1: Correlation between RVSP and V_E/V_{CO_2} for test 1 ($r=0.6$, $p=0.06$)



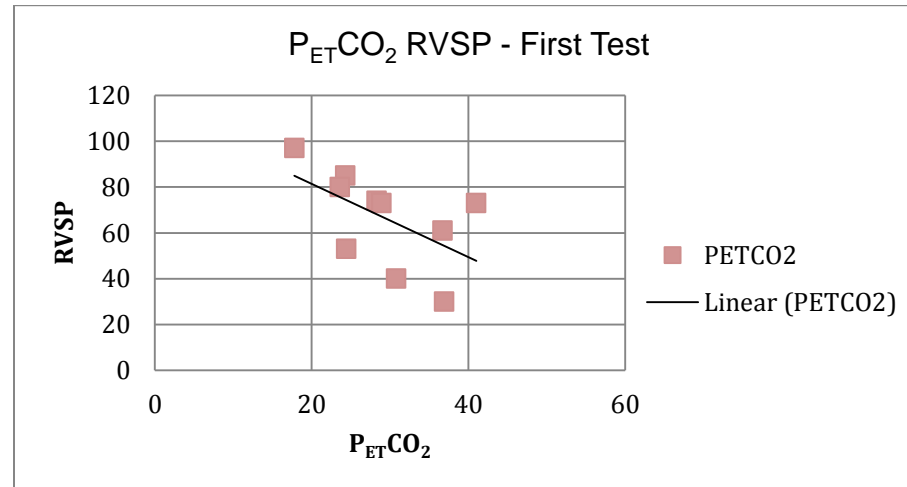
$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide V_E/V_{CO_2} -Ventilatory equivalent ratio for carbon dioxide RVSP-Right ventricular systolic pressure

Figure 2: Correlation between RVSP and V_E/V_{CO_2} for test 2 ($r=0.5$, $p=0.33$)



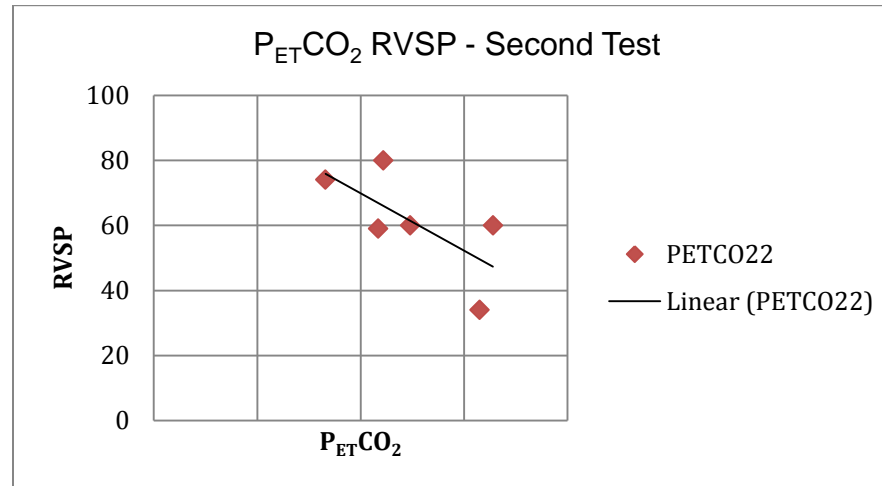
$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide V_E/V_{CO_2} -Ventilatory equivalent ratio for carbon dioxide RVSP-Right ventricular systolic pressure

Figure 3: Correlation between RVSP and $P_{ET}CO_2$ for test 1 ($r=0.6$, $p=0.06$)



$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide V_E/VCO_2 -Ventilatory equivalent ratio for carbon dioxide RVSP-Right ventricular systolic pressure

Figure 4: Correlation between RVSP and $P_{ET}CO_2$ for test 2 ($r=0.7$, $p=0.13$)



$P_{ET}CO_2$ - partial pressure of end-tidal carbon dioxide V_E/V_{CO_2} -Ventilatory equivalent ratio for carbon dioxide RVSP-Right ventricular systolic pressure