THE UTILIZATION OF EXERCISE TESTS IN EVALUATING PATIENTS WITH PULMONARY VASCULAR DISEASE

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**Key words:** pulmonary vascular diseases, primary pulmonary hypertension, Cardiopulmonary Exercise Testing, chronic thromboembolic diseases, Eisenmenger, Riyadh, Saudi Arabia

**Abbreviations used:** (PPH) primary pulmonary hypertension, (E.) Eisenmenger, (CH.TH.EM.) chronic thromboembolic disease, (CO2) carbon dioxide, (COPD) Chronic Obstructive Pulmonary Disease, (CTEPH) chronic thromboembolic pulmonary hypertension, (CPET) Cardiopulmonary Exercise Testing, (VO2 peak) Maximal oxygen uptake, (PAH) pulmonary arterial hypertension, (IPF) Idiopathic pulmonary fibrosis, (VE-/VCO2) ventilatory equivalents for carbon dioxide production, (SpO2) arterial oxygen saturation, (6MWD) 6-min walking distance, (CHF) chronic heart failure, (VE) minute ventilation, (VO2max) maximal oxygen consumption, (VT) volume, (RR) respiratory rate, (PETCO2) end-tidal Pco2, (BTPS) barometric pressure, and water vapor, (SE) standard error, (VE%MVV) maximal ventilation-minute voluntary volume ratio, (PETCO2max) maximal end-tidal pressure for carbon dioxide, (VD/VT) dead-space to tidal volume ratio, (VE/VCO2) ventilatory equivalent ratio for carbon dioxide
Abstract

Purpose: It is known that patients with pulmonary hypertension show an augmented ventilatory response to exercise defined as the slope of minute ventilation over carbon dioxide production (VE/VCO2). We suggested that the degree of ventilatory augmentation may be used to differentiate between patients with primary pulmonary hypertension (PPH), Eisenmenger (E.) and chronic thromboembolic (CH.TH.EM.) disease.

Methods: We retrospectively reviewed the incremental exercise tests of 14 patients with E. disease, 9 patients with PPH and 7 patients with CH.TH.EM disease. These patients had no spirometric evidence of airway obstruction or restriction.

Conclusion: An exaggerated ventilatory response to exercise was found among patients with CH.TH.EM related pulmonary hypertension which is more profound than Eisenmenger and PPH patients. Finding an exaggerated ventilatory response to exercise may suggest CH.TH.EM in patients with pulmonary hypertension and normal spirometry.\(^1\)

\(^1\) Basically hypoxia can be resulted in a significant potentiation of VI that was in which meditate by the act of breathing frequently or constantly.
**Introduction**

Exercise intolerance due to limited oxygen in the blood has been linked to higher mortality rates across a range of diseases. An individual’s inability to meet the energy requirements of a chosen or imposed task generally results in exercise intolerance. The perception of limb fatigue, breathlessness or even pain is noted when there is any impaired function that is affecting the transfer of oxygen from the atmosphere to the contracting muscles. \[^1\] This limited oxygen transfer affects muscles which in turn affects exercise. Respiratory muscle weakness contributes to a variety of issues including hypercapnia – a condition where there is too much carbon dioxide (CO2) in the blood, dyspnoea – shortness of breath, and nocturnal oxygen desaturation. It has also been observed where patients with severe muscle weakness due to steroid-induced myopathy were met with higher mortality rates. In terms of stronger muscles, inspiratory muscle strength has been shown to correlate significantly with walking distance. \[^36\] Exercise intolerance has been shown to be one of the most important predictors of mortality in a broad range of diseases, including COPD, PPH, interstitial lung disease, pulmonary hypertension, chronic heart failure and cystic fibrosis. \[^36\]

The effects of oxygen transfer inability have been shown in a study on cardiopulmonary exercise testing and lung and heart-lung transplantation. Schwaiblmair et al. showed that lung and heart-lung transplant recipients demonstrated severe exercise intolerance prior to transplantation. After transplantation, the same recipients reached maximum oxygen uptakes in the range of 22 to 71% of predicted values. This showed peak oxygen uptake was increased after transplantation. \[^34\]

Exercise testing has been used to show the difference between normal versus abnormal physiological systems. Exercise testing is commonly based on the principle that physiological systems begin to reach their functional limits under stress. Therefore, stressing the organ systems
to a level at which abnormality becomes discernible from the magnitude or profile of response of appropriately selected variables can reflect the capability of those particular systems. \[^1\] Stressing organ systems gradually through increments provides an improved standardized measure. Incremental exercise tests involving gradually added stress which span the entire tolerance range are a commonly accepted measure. The results provide information on normal versus abnormal responses, sites of functional failure, effective operating range of systems, and they also provide a reference for training and rehabilitation. \[^1\] In terms of abnormal information provided, exercise tests have been used as a diagnostic tool for cardiac disease for some time, but in recent years they have become more frequently used in diagnosis and monitoring of pulmonary disorders. Exercise tests diagnose and help understand disease stage severity and are therefore valuable in guiding pharmacological and nonpharmacological treatment and action plans. \[^1\]

In terms of abnormal respiratory information, unexplained dyspnoea during exercise is a frequent reason for exercise testing. Dyspnoea, impaired exercise tolerance and reduced quality of life are common complaints in patients with chronic respiratory disease.\[^36\] Saleemi, in a paper on chronic thromboembolic pulmonary hypertension (CTEPH) explains that CTEPH patients with advanced stages of this respiratory disease experience progressive dyspnoea on exertion, along with other complications. Without intervention, mortality rates are approximately 70%. \[^39\]

Exercise testing is important in both cardiopulmonary and respiratory diseases.

Cardiopulmonary Exercise Testing (CPET) is the standard test used in measuring and assessing exercise tolerance. In healthy children and adults, highly trained athletes, and patients with moderate exercise impairment due to chronic disease, repeated measurements obtained during cardiopulmonary exercise tests have generally shown good reliability and reproducibility. \[^37\] CPET has been advised in a number of conditions including evaluation of exercise tolerance,
evaluation of patients with cardiovascular diseases and evaluation of patients with respiratory
diseases/symptoms. It is considered the gold standard to study a patient's level of exercise
limitation and its causes. The American College of Chest Physicians statement is that CPET
provides a more global assessment of integrative exercise responses which measurement of
individual organ system functions does not provide. It is because of this that CPET is gaining
widespread clinical usage for evaluating undiagnosed exercise intolerance. This in turn has led to
increasingly acceptance for CPET in patient management. It has been found that health status
correlates better with exercise tolerance rather than with resting measurements. CPET should be
considered when specific questions remain unanswered after consideration of basic clinical data
such as patient history, and physical examination. With CPET a wide variety variables can be
measured. [30]

A study by Hansen et al. questioned whether severe disability such as heart failure, could increase
variability and decrease the confidence interpretation of CPET key measurements. The study
found high reproducibility of the key physiologic measurements as was found in other studies
involving heart, lung, musculoskeletal, and renal disease with less severe exercise impairment.
The study concluded that well-conducted gas exchange exercise tests can safely and reliably
measure key and discriminating exercise variables, including VO$_2$ peak, in moderately to very
severely impaired children and adults. VO$_2$ peak is the highest level of oxygen uptake at peak
exercise during test performance. Taken alone, a change in VO$_2$ peak of 8 to 10% might be used as
a cut off in deciding that there is a significant change in exercise tolerance. [37]

The patients in this study with pulmonary arterial hypertension (PAH) appear to be more
impaired than those in any previously report CPET reproducibility study of patients with either
cardiovascular or pulmonary diseases. In using CPETs to evaluate and follow up PAH patients,
these tests were used to assess patient performance variability and evaluate reading variability. This study found that CPET measurements can be safely, reliably, and reproducibly assessed even in patients with severe exercise intolerance.

CPET is increasingly being used for the clinical evaluation of patients with respiratory diseases. [12] Idiopathic pulmonary fibrosis (IPF), a progressive form of lung disease, is characterized by progressive dyspnoea and impaired gas exchange which lead to mortality. In a study on the prognostic value of cardiopulmonary exercise testing in idiopathic pulmonary fibrosis, Flaherty hypothesized that maximal oxygen uptake during cardiopulmonary exercise testing would predict mortality in IPF patients. The mean survival from time of diagnosis to death is three years. The study found that in IPF, gas exchange worsens with exercise. The study concluded that maximal oxygen uptake below 8.3 ml/kg/min during CPET increased risk of death for patients with IPF. [40] Lung transplantation, for IPF patients under 55 years of age and without complicating medical illness, is a viable option. [38]

CPET results show the pattern of deviation of abnormal response from the normal response and therefore indicate impairments of physiological systems based on pattern of abnormality. [11]

Exercise indices have been shown to be better indicators of health than resting measures. Exercise indices such as VO$_2$ peak; ventilatory equivalents for carbon dioxide production (V$_{E}$/VCO$_2$) which indicate how many liters of air breathed to eliminate 1 liter of CO2; and arterial oxygen saturation (S$_p$O$_2$) which indicates an estimation of arterial hemoglobin oxygen saturation, have in fact proven to be better predictors of prognosis than lung function measurements obtained at rest. [3] In sports medicine, criterion used to define a subject’s exercise capacity has classically been based on VO$_2$ peak standardized by weight where in normal values for healthy young adults is in the
range of 35-45 mL·min⁻¹·kg⁻¹.\textsuperscript{[33]}

Exercise tolerance is known to be a predictor of mortality in patients with pulmonary and cardiovascular disease. In PPH specifically, exercise indices that have been shown to predict prognosis of patients include \(VO_2\text{ peak}\), arterial desaturation, and 6-min walking distance (6MWD). \(VO_2\text{ peak}\) has been reported as a significant predictor of survival in PPH. \(VO_2\text{ peak}\) less than or equal to 10.4 mL·min⁻¹·kg⁻¹ is associated with a 50% risk of death at 1 yr and this significantly increases in the second year; however, the risk decreases to 10% at 1 yr and 30% in the second year if \(VO_2\text{ peak}\) is greater than 10.4 mL·min⁻¹·kg⁻¹. Adding peak systolic blood pressure into the equation increased the predictive value of \(VO_2\text{ peak}\) where patients with a \(VO_2\text{ peak}\) less than or equal to 10.4 mL·min⁻¹·kg⁻¹ and a peak systolic blood pressure of less than 120 mmHg have a worse prognosis than those with only one of the two risk factors. Patients with PPH showed that the 6MWD correlates well with \(VO_2\text{ peak}\) where patients who walked greater than 332 meter had a 90% survival rate as compared to those who walked less than 332 meters who had a survival rate of 20%. Overall, higher levels of oxygen in the blood equated to higher chances of survival; therefore, the evaluation of exercise tolerance through CPET and the 6MWT in patients with lung and heart disease is of great prognostic value.\textsuperscript{[32]}

We suggest that the degree of ventilatory augmentation may be used to differentiate between patients with primary pulmonary hypertension (PPH), Eisenmenger (E.) and chronic thromboembolic (CH.TH.EM) disease. Abnormalities in cardiopulmonary responses to incremental cycle ergometer exercise are often similar in obstructive, restrictive and pulmonary vascular disorders. All are characterized by an accelerated ventilatory response, primarily as a result of the effects of high fixed physiological dead space, combined, in many cases with attendant arterial oxygen desaturation. The breathing pattern is more rapid and shallow in both
obstructive and restrictive lung disorders compare to health. In general, respiratory frequency responses to exercise are most pronounced in patients with restrictive lung disease.

Exercise testing along with respiratory measurements may gain more insight into disease. Symptoms scores for dyspnoea and exertion have been shown to be valuable tools during exercise testing, at both peak exercise and specific time points during testing. Exercise is often limited by intolerable symptoms of dyspnoea, leg discomfort or a combination of both of these well before the physiological boundaries of the respiratory and cardiovascular systems are reached. Dyspnoea is connected with physical activity therefore it is necessary to understand methods for assessing symptoms associated with exercise.

^Dyspnoea is the act of breathing difficultly, and can be often caused by Asthma, Smoking, Excessive Exercise, Obesity, etc.

^3 When the boundaries of your cardiovascular system are reached means most likely the point of VO2 Max, this is the point of the maximum oxygen intake from extensive exercise that starts a point of Dysponea.
Literature Review

Pulmonary hypertension has been defined as a mean Ppa of >25 mmHg at rest or >30 mmHg during exercise.\textsuperscript{[4]} Pulmonary hypertension is noted to be consistently associated with reduced exercise capacity wherein it has recently been shown that peak V’O\textsubscript{2} correlates significantly with New York Heart Association symptom class in patients with primary pulmonary hypertension.\textsuperscript{[5, 6]} Patients with pulmonary hypertension are noted to have both resting hyperventilation and also excessive ventilation for any given exercise load.\textsuperscript{[7, 8] }CPET can uncover abnormalities in the integrated functions of the cardiovascular, respiratory, metabolic, peripheral muscle and neurosensory systems. The ventilatory response to exercise is usually abnormal across the spectrum of more advanced pulmonary disorders. Ventilatory index is used in assessment of Ventilatory limitation.\textsuperscript{[12]}

In patients with chronic heart failure (CHF), several observations relate heart failure severity to hyperventilation. Hyperventilation is associated with dyspnoea, one of the most common symptoms of CHF. An abnormally increased minute ventilation (VE) – volume of air exhaled from the lungs in 1 minute – requirement is one of the limiting factors of exercise capacity. And a low ventilatory efficiency which is high VE when compared to V\textsubscript{CO\textsubscript{2}} is a strong negative prognostic predictor, independent of VO\textsubscript{2 peak}. Hyperventilation during exercise in CHF may be due to alteration in lung mechanics, reduced lung diffusion, and increased ventilatory requirements. In CHF patients compared with healthy individuals, CPET typically reveals reductions in VO\textsubscript{2 peak}. CPET is a very important tool in assessing the prognosis of cardiac patients and choosing effective treatment. CPET is useful in evaluating the degree of exercise limitation and identifying underlying causes.\textsuperscript{[35]}
Patients with obstructive lung disease exhibit several ventilatory abnormalities such as an increased dead space ventilation, a reduced ventilatory reserve, an increased work of breathing, and mechanical problems related to the position of the diaphragm. The factors that contribute to dyspnoea in patients with pulmonary disorders such as COPD are related to a combination of high ventilator requirement coupled with low ventilatory capacity.

Pulmonary hypertension should be suspected when ventilatory responses to exercise are abnormally elevated in the presence of relatively preserved spirometric parameters.

The maximal oxygen consumption (VO2max) is considered to provide an index of severity wherein it is noted to be lower in patients with high pulmonary vascular resistance and lower cardiac index. Further, it is also significantly correlated with the amount of functional vascular bed. Reductions in VO2 peak reflected reduced cardiac output according to the study conducted on patients with primary pulmonary hypertension. Studies have indicated that non-hypoxic pulmonary hypertension patients have a greater exercise capacity and a larger SLOPE (VE/VCO2) which reflects worsened ventilation–perfusion inequality.

The slope of VE/VCO2 is consistently elevated when compared to health, as is the ventilator equivalent at the ventilatory threshold. Studies have also indicated that the VE/VCO2 ratio correlates well with hemodynamic indices of pulmonary hypertension.

The measurements of the ventilatory response to exercise were suggested as a noninvasive screening test for pulmonary hypertension. The 6-min walk test (6MWT) and CPET are currently proposed for diagnostic, therapeutic and prognostic finalities of pulmonary vascular disorders. Field testing and incremental exercise testing have complementary value in assessment for pulmonary rehabilitation. The 6MWT is easy to perform and is attractive as it is more relevant
As a field test, due to its simplicity and inexpensive nature, the 6MWT is gaining widespread usage in identifying an individual’s functional capacity and exercise limitation, and is determining intervention. Since walking is a common form of activity for most people, walk tests are favorable for usage among elderly and frail populations, of whom make up the majority of patients with chronic respiratory and cardiac disease. As walk test standardization improves, field test information derived from walk test is expected to be optimized. \[^{31}\]

Considered an incremental test, CPET is thought to be highly reproducible and provides remarkable insights into the pathophysiological mechanisms that lead to exercise intolerance. \[^{17}\]
This incremental exercise test is the standard test used when studying cardiovascular, pulmonary and metabolic adaptations to exercise in cardiac patients. The majority of cardiopulmonary exercise tests in cardiac diseases are performed in patients with chronic heart failure. \(\text{VO}_2\text{peak}\) is the most well known and widely used variable obtained from CPET. \(\text{VO}_2\text{peak}\) less than 10 mL·min·kg\(^{-1}\) is associated with poor prognosis, while \(\text{VO}_2\text{peak}\) greater than 16 mL·min·kg\(^{-1}\) is associated with good prognosis. \[^{35}\]
Material and methods

Subjects

We retrospectively reviewed the incremental exercise tests of 14 patients with E. disease, 9 patients with PPH and 7 patients with CH.TH.EM disease.

Study Protocol

The study protocol involved the performance of baseline pulmonary function tests as well as maximal symptom-limited incremental exercise on cycle ergometer. Ergometry assesses exercise capacity in order to determine level of exercise intolerance, identify contributing factors of exercise limitation, and investigate risk of exercise.\(^{[36]}\)

Spirometry was performed with the subject in a seated position with a calibrated electronic spirometer (System 1070 Medical Graphics Corporation, St. Paul, Minn). Lung volumes were determined by body box plethysmography (PK Morgan Limited, England). Maximum voluntary ventilation was measured as previously described.\(^{[18]}\)

Exercise was performed on an electrically braked cycle ergometer (Mijnhardt) with stepwise increasing workloads of 15 W every 2 min. Subjects were seated, wore a nose clip, and breathed through a mouthpiece into a modified low-resistance two-way valve (model 6115, Hans Rudolph Inc, Kansas City, Mo). Expiratory gases were analyzed breath by breath with a computerized exercise system (System 2001, Medical Graphics Corporation, St. Paul, Minn). The breath-by-breath signal was integrated by the system computer to yield 15-s moving averages of minute ventilation (VE), tidal volume (VT), respiratory rate (RR), VO\(_2\), VCO\(_2\), and end-tidal Pco\(_2\) (PETCO\(_2\)) Air flow and gas measurements were corrected for ambient temperature, barometric pressure, and water vapor, and expressed in BTPS units. Exercise equipment was calibrated prior
to each study with gases of known concentrations and a 3-L calibration syringe.

Determinations of levels of dyspnoea were obtained by having the subjects rate their "degree of shortness of breath" according to the modified Borg scale (0 = none to 10 = maximal dyspnoea). [19]

Mean values of pulmonary are reported as mean ± standard error (SE) of the mean. Ninety-five percent confidence limits for normal control subjects were established as previously described. [20] Regression lines for exercise relationships were determined by least squares method. [20]

Results

The data from the three subject groups has been summarized in tables 1 and 2. The study included 14 patients with E. disease, 9 patients with PPH and 7 patients with CH.TH.EM. disease. The patients suffering from Eisenmenger disease and PPH were in their middle age, while the patients with CH.TH.EM. were in their early 50s. The predicted percentages of $F_{ev1}$, $F_{vc}$, and TLC were almost equivalent across the three groups. These patients had no spirometric evidence of airway obstruction or restriction. VE/VCO2 max was significantly higher in the CH.TH.EM (78.8 ± 10.3) compared to Eisenmenger (60.3 ± 4.1) and PPH (56.8 ± 6.9) groups. The exercise parameters revealed some significant results. The VO2max% in subjects with CH.TH.EM (73.0± 32.6) was significantly higher than the E (43.7 ± 6.2) and PPH (41.0±10.3) subjects.
Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eisenmenger</th>
<th>PPH</th>
<th>CH.TH.EM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35.6 ± 2.9</td>
<td>38.1 ± 3.2</td>
<td>50.0 ± 6.1</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>82.1 ± 4.6</td>
<td>80.6 ± 4.2</td>
<td>84.3 ± 9.5</td>
</tr>
<tr>
<td>TLC%pred</td>
<td>100 ± 2.9</td>
<td>93.5 ± 4.6</td>
<td>89.3 ± 13.2</td>
</tr>
</tbody>
</table>

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Table 1- Baseline Characteristics

There were no significant differences in most of the other values such as the Max VE%MVV, VTmax, Max Resp. rate and PETCO2max. Some amount of difference was noted in the VD/VTmax between the CH.TH.EM, E and PPH groups but the values were not significant.

However, VO2/h rate max and VE/VCO2 max were significantly higher in CH.TH.EM. (11.9 ± 6.2 & 78.8 ± 10.3) compared to Eisenmenger (5.9 ± 0.7 & 60.3 ± 4.1) and PPH (5.6 ± 1.0 & 56.8 ± 6.9) groups.
Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eisenmenger</th>
<th>PPH</th>
<th>CH.TH.EM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2max%pred</td>
<td>43.7 ± 6.2</td>
<td>41.0±10.3</td>
<td>73.0± 32.6</td>
</tr>
<tr>
<td>Max VE%MVV</td>
<td>53.1 ± 6.1</td>
<td>49.8±5.6</td>
<td>50.0± 6.41</td>
</tr>
<tr>
<td>VTmax, liter</td>
<td>1.30 ± 0.1</td>
<td>1.25 ± 0.1</td>
<td>1.20± 0.05</td>
</tr>
<tr>
<td>Max Resp. rate</td>
<td>35.9 ± 2.0</td>
<td>34.0 ± 3.5</td>
<td>39.6 ± 3.9</td>
</tr>
<tr>
<td>PETCO2max</td>
<td>21.2 ± 1.26</td>
<td>24.4 ± 2.9</td>
<td>18.9 ± 3.3</td>
</tr>
<tr>
<td>VD/VTmax%</td>
<td>22.5 ± 1.5</td>
<td>23.6 ± 2.5</td>
<td>30.1 ± 2.0</td>
</tr>
<tr>
<td>VO2/h. rate max</td>
<td>5.9 ± 0.7</td>
<td>5.6 ± 1.0</td>
<td>11.9 ± 6.2</td>
</tr>
<tr>
<td>VE/VECO2 max</td>
<td>60.3 ± 4.1</td>
<td>56.8 ± 6.9</td>
<td>78.8 ± 10.3</td>
</tr>
</tbody>
</table>

Table 2: lists the exercise parameters (Values are means ± SE.)

Discussion

Pulmonary thromboembolic disease has been noted to have a wide variety of clinical presentations. The spectrum of thromboembolic diseases can range from acute minor pulmonary embolism to chronic thromboembolic pulmonary hypertension. [21]

The VO2max% in subjects with CH.TH.EM (73.0± 32.6) disease was noted to be significantly higher than the E (43.7 ± 6.2) and PPH (41.0±10.3) subjects. This was evident although other parameters such as the Max VE%MVV, VTmax, Max Resp. rate and PETCO2max were not different amongst all the three groups. Excessive ventilation is generally attributed either to an increase in the dead space ventilation (inadequate perfusion of ventilated lung areas) or to
alveolar hyperventilation due to a decreased PaCO2 set point.\textsuperscript{[6]}

Pulmonary embolism has been noted to result in an abnormal alveolar dead space that is expired in synchrony with gas from normally perfused alveoli. This feature of pulmonary embolism separates the condition from other pulmonary diseases affecting the airways, which are characterized by nonsynchronous emptying of compartments with an uneven ventilation/perfusion relationship.\textsuperscript{[22, 23]}

The VD/Vtmax scores were also comparatively higher in CH.TH.EM. disease than others. It has been demonstrated that the increase in physiologic dead space to tidal volume (VD/VT) had comparable sensitivity and specificity to radioisotope scanning in the diagnosis of pulmonary emboli. The high VD/VT leads to high dead space ventilation.\textsuperscript{22} The VE/VCO2 ratio will be higher than the normal when the VD/VT ratio is high or the patient hyperventilates.\textsuperscript{24}

Maximal O2 utilization has been noted to be directly proportional to the maximal level of cardiac output. On the other hand, it is inversely proportional to the pulmonary vascular resistance and the level of pulmonary arterial pressure.\textsuperscript{[13]} Janicki et al concluded that determination of VO2 max had a potential of becoming the practical screening method for the identification and prediction of the severity of pulmonary vascular diseases.\textsuperscript{[13]}

The ventilatory and/or circulatory disturbances present in patients with chronic lung disorders impair the response to exercise.\textsuperscript{[25]} The response to a standard exercise regimen across different individuals can vary according to the load in relation to the maximum load an individual can tolerate. Thereby, maximum workload expressed as VO2 max can be studied to differentiate the chronic lung disorders. A high oxygen pulse at VO2 max, according to studies can rule out severe pulmonary artery hypertension.\textsuperscript{[25]}
It is widely known that exercise results in abnormally large increases in the pulmonary artery pressure in individuals suffering from pulmonary vascular disease.\(^{[26]}\) Studies have noted that VO2 kinetics may be limited by pulmonary hemodynamics in the presence of disease.\(^{[27]}\)

Further, it was also noted that the VO2/h rate max was significantly higher in CH.TH.EM. (11.9 ± 6.2) compared to Eisenmenger (5.9 ± 0.7) and PPH (5.6 ± 1.0) groups. A significant difference was also noted in the VE/VCO2 scores. Thereby, an exaggerated response becomes evident with the finding that although there was not much difference in the Max VE%MVV, VTmax, Max Resp. rate and PETCO2max scores, the VO2 and VE/VCO2 were significantly higher in subjects with CH.TH.EM disease.

The partial pressure of end-tidal carbon dioxide (PETCO2max) was comparatively lower in subjects with CH.TH.EM disease. Studies have demonstrated that abnormally high positive arterial to end-tidal PCO2 difference at rest almost completely separates patients with pulmonary embolism from those without. However, a high degree of overlap with patients with obstructive or restrictive lung disease may be noted.\(^{[28]}\) Nevertheless, if the positive arterial to end-tidal PCO2 remains positive during exercise, this is evidence for decreased perfusion to ventilated alveoli.\(^{[29]}\) Further, it should be noted that PETCO2 is lower than PaCO2 in diseases with ventilation-perfusion mismatching.\(^{[24]}\)

Our study demonstrated that the ventilatory responses were altered in patients with pulmonary hypertension, Eisenmenger disease and chronic thromboembolic disease. Further, it was also noted that VE/VCO2 max was significantly higher in the CH.TH.EM. (78.8 ± 10.3) compared to Eisenmenger (60.3 ± 4.1) and PPH (56.8 ± 6.9) groups. Janicki and colleagues demonstrated using cardiopulmonary exercise testing that the peak exercise oxygen consumption (peak VO2)
was decreased and the regression slope relating minute ventilation to carbon dioxide output (VE-VCO2 slope) was increased in patients with chronic thromboembolic disease. \cite{5} Thereby the findings from our studies suggest that exaggerated ventilatory response to exercise may suggest CH.TH.EM in patients with pulmonary hypertension and normal spirometry.

**Conclusion**

An exaggerated ventilatory response to exercise was found among patients with CH.TH.EM related pulmonary hypertension which is more profound than Eisenmenger and PPH patients. Finding an exaggerated ventilatory response to exercise may suggest CH.TH.EM in patients with pulmonary hypertension and normal spirometry.
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