

# A comparison of pattern of breathing during incremental exercise in patients with pulmonary fibrosis and primary pulmonary hypertension

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**Abstract:** It has previously been proposed that the pattern of breathing during exercise, and particularly maximum tidal volume, can be used to distinguish between interstitial lung disease and pulmonary vascular disease; however this has never been formally investigated. This study looks at the impact of incremental exercise on a bicycle ergometer and the impact that such exercise has on breathing pattern, specifically maximum tidal volume. Method: We retrospectively reviewed the incremental exercise tests of 10 patients with pulmonary fibrosis (PF) and 9 with primary pulmonary hypertension (PPH). Patients were exercised using a bicycle ergometer, seated, and breathing into a mouthpiece. Results: The VE/VCO<sub>2</sub> relationship was linear in all patients, but PPH patients had higher VE/VCO<sub>2</sub> slopes (0.058±0.03) mean ±SD than PF patients (0.039±0.01, P<0.04). The respiratory rate/VE slopes were also higher in PPH patients (0.48±0.17) than in PF patients (0.30±0.14, P<0.02). There was no correlation between the VTmax/IC at the end of exercise and the IC %predicted in either group. However, VTmax as % of IC at the end of exercise in PPH patients (59.1±7.6) was lower than in PF patients (87.0±14.5%, P<0.001). Conclusion: The pattern of breathing during exercise, specifically maximum tidal volume, is different in patients with primary pulmonary hypertension compared with pulmonary fibrosis patients. These changes in the breathing pattern are unrelated to underlying static and dynamic lung function. Thus, the conclusion is that patients who have lung diseases which restrict their breathing often compensate, likely in an effort to avoid dyspnea, by modifying their natural breathing into a more tightly constrained pattern.

**Keywords:** Pulmonary Vascular Diseases, Primary Pulmonary Hypertension, Cardiopulmonary Exercise Testing, Chronic Thromboembolic Diseases, Eisenmenger, Riyadh, Saudi Arabia

## 1. Introduction

It has previously been proposed that the pattern of breathing during exercise and particularly maximum tidal volume can be used to distinguish between interstitial lung disease and pulmonary vascular disease; however this has never been formally investigated.

Method: we retrospectively reviewed the incremental exercise tests of 10 patients with pulmonary fibrosis (PF) and 9 with primary pulmonary hypertension (PPH).

Results: The VE/VCO<sub>2</sub> relationship was linear in all patients, but PPH patients had higher VE/VCO<sub>2</sub> slopes (0.058±0.03) mean ±SD than PF patients (0.039±0.01, P<0.04). The respiratory rate/VE slopes were also higher in PPH patients (0.48±0.17) than in PF patients (0.30±0.14, P<0.02). There was no correlation between the VTmax/IC at the end of exercise and the IC %predicted in either group. However, VTmax as % of IC at the end of exercise in PPH patients (59.1±7.6) was lower than in PF patients (87.0±14.5%, P<0.001).

In conclusion, the pattern of breathing during exercise,

specifically maximum tidal volume, is different in patients with primary pulmonary hypertension compared with pulmonary fibrosis patients. These changes in the breathing pattern are unrelated to underlying static and dynamic lung function.

## 2. Material and Methods

### 2.1. Subjects

In this studied we reviewed the results of an incremental exercise stress test in ten patients who presented with sarcoidosis; these results were compared to the results of nine control subjects on the same test. Baseline pulmonary function was tested, in addition to maximal symptom-limitations measured through incremental exercise, using a bicycle ergometer.

### 2.2. Pulmonary Function Tests

A calibrated electronic spirometer (System 1070 Medical Graphics Corporation, St. Paul, MN, USA) was used was used to measure spirometry of the subject while in a seated position. Lung volume was also measured, using body box plethysmography (PK Morgan Limited, Kent, UK), and maximum voluntary ventilation measured as described in the literature previously<sup>[13]</sup>. During the study we recorded these variables: forced vital capacity (FVC, measured in liters), forced expiratory volume over 1 second (FEV<sub>1</sub>, measured in liters), diffusion capacity for carbon monoxide (DL<sub>CO</sub>), and total lung capacity (TLC).

### 2.3. Incremental Exercise Testing

We conducted an incremental symptom-limited exercise test using an electrically braked bicycle ergometer (Mijnhardt, KEM3). Subjects took the test while seated, wearing a clip on their nose, and breathing through a modified low-resistance, two-way valve mouthpiece (model 6115, Hans Rudolph Inc., Kansas City, MO, USA). During the test stepwise workloads were increased 15 Watts every two minutes. A computerized exercise system measured breath, analyzing the expiratory gases (System 2001, Medical Graphics Corp., St. Paul, MN, USA). The computer system used a breath-by-breath signal to calculate the 15-s moving averages per minute of ventilation (VE), respiratory rate (RR), tidal volume (VT), and VO<sub>2</sub>. The exercise equipment was calibrated before each use, using a 3-L calibration syringe and a combination of gases with specific concentrations. We corrected gas and air flow measurements for the following: ambient temperature, barometric pressure, water vapor; these measurements were expressed in bag body temperature and pressure saturated (BTPS) units.

We categorized resting functional variables using commonly adopted cutoff points in the percent that was predicted. The difference in value of anticipated total lung capacity (TLC) and anticipated functional residual capacity (FRC) was determined find the IC. On a continuing basis

measurements were taken for arterial pressure, heart rate and oxygen saturation. We calculated the dyspnea levels of each subject using an adjusted Borg scale (0 = none to 10 = maximal dyspnea)<sup>[14]</sup>. Patients were taught how to use the Borg scale and then asked to rate the “degree of shortness of breath” that they experienced during the treatment.

## 3. Results

**Table 1.** Baseline Characteristics and -Exercise Parameters

	PF	PPH	p-Value
Age	60.5±2.4	38.1±3.0	.001
FEV <sub>1</sub> %pred	78.8±4.8	80.6±3.9	NS
FVC%pred	67.4±3.1	79.1±4.5	NS
IC%pred	64.0±5.2	84.3±4.8	<.05
VO <sub>2</sub> max%pred	71.5±7.14	40.6±6.6	<.05
Peak V <sub>E</sub> %MVV	68.3±4.1	44.6±5.7	<.05
V <sub>T</sub> max,l	1.57±0.11	1.23±0.95	<.05
Peak RR/min	39.9±1.6	34.0±3.44	NS

Parameters (Values are means ± SE.)

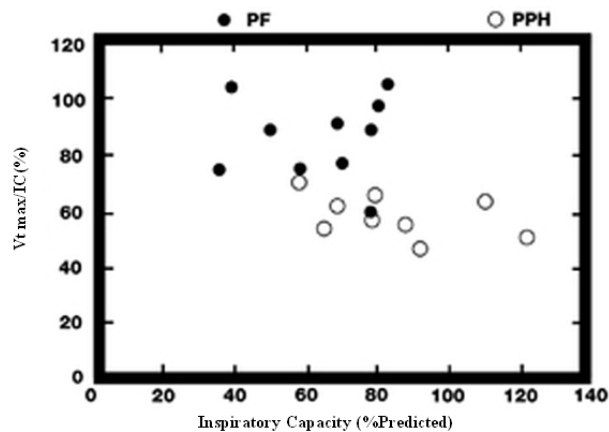
The VE/VCO<sub>2</sub> relationship was linear in all patients, but PPH patients had higher VE/VCO<sub>2</sub> slopes (0.058±0.03) mean ±SD than PF patients (0.039±0.01, P<0.04). The respiratory rate/VE slopes were also higher in PPH patients (0.48±0.17) than in PF patients (0.30±0.14, P<0.02). There was no correlation between the VTmax/IC at the end of exercise and the IC %predicted in either group (figure 1). However, VTmax as % of IC at the end of exercise in PPH patients (59.1±7.6) was lower than in PF patients (87.0±14.5%, P<0.001), (figure 2).

## 4. Discussion

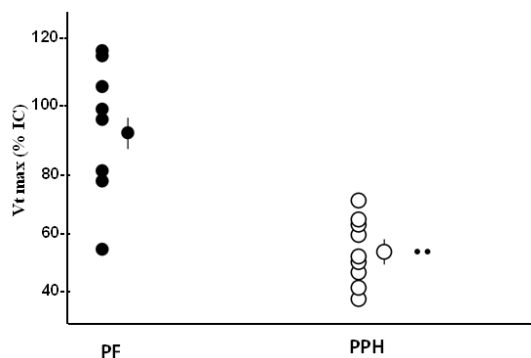
We retrospectively reviewed the incremental exercise tests of 10 patients with pulmonary fibrosis (PF) and 9 with primary pulmonary hypertension (PPH). Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing lung disease predominantly a disease of patients over 50 who typically present with exertional dyspnea and a nonproductive cough. An independent risk factor for development of idiopathic pulmonary fibrosis may be smoking of cigarettes. Surgical lung biopsy reveals the histologic development of usual interstitial pneumonia (UIP). Idiopathic pulmonary fibrosis is an illness that progresses over time. As parenchymal fibrosis advances it results in decreased lung function which causes breathing to become progressively more difficult. The estimated prevalence in the United States is between 35,000 and 55,000 cases. The median survival time for patients with IPF is less than 3 years, while 5%-10% survive 10 years. Statistics reveal that about 40% of people with IPF die, eventually, as a result of failure of the lungs. No proven therapies exist; treatment is mainly supportive<sup>[4]</sup>.

Pulmonary hypertension (PH) is a progressive, nearly

always fatal condition. Morbidity and mortality are due to failure of right ventricular compensation for increased afterload caused by obstructive pulmonary arterial remodeling<sup>5</sup>. It is characterized by the deregulated proliferation of pulmonary artery endothelial cells and intimal smooth muscle cells, both resistant to cellular apoptosis. Right heart catheterization is essential to confirm diagnosis, determine prognosis, and assign therapy<sup>6</sup>. Early symptom recognition in high-risk groups is essential for earlier diagnosis and treatment.



**Figure 1.** There was no relationship between  $V_{max}/IC$  and resting inspiratory capacity in all patients



**Figure 2.** Patients with primary hypertension developed smaller  $V_{max}/ratio$  than those with pulmonary fibrosis.

Pulmonary function tests in IPF patients show a restrictive pattern of disease manifested in reduced measures of lung capacities and volumes, such as total lung capacity (TLC), functional residual capacity (FRC), vital capacity (VC), and residual volume (RV). Blood gas measurements reveal a reduced  $PaO_2$  value with a low  $PaCO_2$  measurement attributable to ventilation/perfusion mismatching. During exercise hypoxaemia is exacerbated and a widening of the alveolar-arterial (A-a) gradient is observed. Lung function tests (including gas transfer measurements) should be made repeated at 3 monthly intervals during the first year and less frequently thereafter to assess the progression of the disease process.<sup>7</sup>

Exercise testing has, therefore, found a place in the diagnosis and monitoring of patients with IPF. Exercise desaturation can suggest early stages of interstitial lung

disease and pulmonary hypertension, or late stages of obstructive lung diseases, such as COPD and emphysema.

The utility of a pulmonary function tests goes beyond diagnosis and functional capacity. Exercise-induced hypoxia is also an index of the severity of interstitial lung disease and can define prognosis in terms of mortality.<sup>8</sup>

Fell et al (2009) found evidence that peak  $VO_2$  measured during incremental cardiopulmonary exercise testing is a useful prognostic indicator of survival in patients with Pulmonary Fibrosis. Patients with  $VO_{2max}$  less than 8.3 ml/kg/min at baseline had an increased risk of death.<sup>9</sup>

Cardiopulmonary exercise testing (CPET) allows for dynamic, largely noninvasive, evaluation which includes both peak and submaximal impacts of exercise. CPET has become more and more respected for use in a variety of clinical tests and settings, often used to look at exercise intolerance and related symptoms in an effort to determine the specific impairment and functional capacity. In most clinical circumstances, cycle ergometry is the preferable mode of cardiopulmonary exercise. Its main advantage is easily and direct quantification of the work rate performed, by the use of electrically braked cycles which increase resistance to pedaling electro magnetically and computer controlled allowing the work rate to be incremented automatically and even continuously [10]. An incremental exercise test provides a smooth gradational stress which typically spans the entire tolerance range. Incremental protocol is most widely used in clinical practice.

#### 4.1. CPAT Measurements

CPET is effective in the early detection of subtle pulmonary gas exchange abnormalities not revealed by routine testing. This is important in establishing a timely diagnosis and accurate physiologic severity assessment, as well as in permitting the monitoring of therapeutic intervention.

Many variables are measured or derived during CPET: oxygen uptake ( $Vo_2$ ), carbon dioxide output ( $V_{co_2}$ ), and minute ventilation ( $V_e$ ), in addition to monitoring electrocardiography, blood pressure, and pulse oximetry, typically during a symptom-limited maximal progressive exercise tolerance test.

Exercise tolerance is a reflection of how long a patient is able to sustain a particular activity, and is well recognized as a good predictor of mortality for a wide range of pulmonary and cardiovascular disease states. A reduced  $Vo_2$  peak is the starting point in the evaluation of reduced exercise tolerance. Studies confirm CPET can be performed safely on patients with primary pulmonary hypertension in which reductions in  $Vo_2$  peak reflect reduced cardiac output and functional capacity.<sup>11</sup>

The ratio of  $V_e$  to  $V_{co_2}$  is called the ventilatory equivalent for  $CO_2$ , related to the tidal volume, being higher as tidal volume increases. The normal subsequent increase in  $V_e/V_{co_2}$  reflects the onset of compensatory hyperventilation for metabolic acidosis. Lack of a subsequent increase  $V_e/V_{co_2}$  reflects either insensitivity to

the stimuli associated with metabolic acidosis or the presence of high airway resistance or a general increase in respiratory muscle load. This may be observed in some patients who are ventilatory limited.

Patient's endurance capacity in the cycle ergometer test can be the measurement at time to symptom limitation of the CPET variable expressed by the slope of the linear region of the minute ventilation ( $\dot{V}_E$ )–carbon dioxide output ( $\dot{V}_{CO_2}$ ) relationship<sup>12</sup>

This was apparent in our results in which the  $\dot{V}_E/\dot{V}_{CO_2}$  relationship was linear in all patients, however the PPH patients had higher  $\dot{V}_E/\dot{V}_{CO_2}$  slopes than PF patients as well as the higher respiratory rate/ $\dot{V}_E$  slopes in PPH patients compared to PF patients. This is significant since the degree to which tidal volume influences the expiratory flow volume is an indicator for the amount of expiratory flow limitation. End-expiratory lung volume (EELV) typically begins to increase as work rate and ventilatory requirements increase in patients who begin to develop significant expiratory flow limitation. By taking into consideration the patient's breathing strategy (tidal volume), operational lung volume (EELV), and exercise-induced changes in airway tone performed during exercise, maximal available ventilation can be determined. The ventilatory responses to muscular exercise, including its breathing pattern and airflow profile components, provide important information for interpretation of clinical exercise testing<sup>10</sup>

Patients afflicted with restrictive lung disease often experience a decrease in their lung elasticity; this makes deep breathing challenging. These people often compensate through more shallow breathing, in order to avoid dyspnea. When tidal volume deviates from average resting volume the stimulation of one, or two, sets of receptors in the respiratory muscles can lead to dyspnea. Specifically, low tidal volume can stimulate muscle spindles, while high tidal volumes can stimulate tendon organs.

Thus, the conclusion is that patients who have lung diseases which restrict their breathing often compensate, likely in an effort to avoid dyspnea, by modifying their natural breathing into a more tightly constrained pattern<sup>[13]</sup>.

CPET variables have been proven useful in the prognostic evaluation of interstitial lung disease and primary pulmonary hypertension, as well as candidacy for transplantation and thoracic surgical procedures. Therefore, there is a major indication for exercise testing in these patient groups. Exercise tolerance and other CPET indices (as the  $\dot{V}_E/\dot{V}_{CO_2}$  slope) appear to be better predictors of prognosis than resting lung function<sup>12</sup>

## 5. Conclusion

The pattern of breathing during exercise, specifically maximum tidal volume, is different in patients with primary pulmonary hypertension compared with pulmonary fibrosis patients. These changes in the breathing pattern are unrelated to underlying static and dynamic lung function

## 6. Abbreviations Used

(6MWD) 6-min walk distance, (6MWT) 6-min walk test, (A-a) alveolar-arterial gradient, (BTPS) body temperature and pressure saturated, (CPET) Cardiopulmonary exercise testing, (DLCO) diffusion capacity for carbon monoxide, (DSP) distance saturation product, (EELV) End-expiratory lung volume, (FEV1) forced expiratory volume over 1 second, measured in liters, (FRC) functional residual capacity, (IPF) Idiopathic pulmonary fibrosis, (mPAP) mean pulmonary arterial pressure, (IC) inspiratory capacity, (NYHA) New York Heart Association Functional Classification, (PF) pulmonary fibrosis, (PH) Pulmonary hypertension, (PPH) primary pulmonary hypertension, (RV) residual volume, (sPAP) systolic pulmonary arterial pressure, (TLC) total lung capacity, (TLC) total lung capacity, (FRC) functional residual capacity, (UIP) usual interstitial pneumonia, ( $\dot{V}_{CO_2}$ ) carbon dioxide output, (VC) vital capacity, ( $\dot{V}_E$ ) minute of ventilation, (RR) respiratory rate, ( $\dot{V}_E$ ) minute ventilation, ( $\dot{V}_{O_2}$ ) oxygen uptake, (VT) tidal volume, (FVC) forced vital capacity, measured in liters, ( $\dot{V}_E/\dot{V}_{CO_2}$ ) ventilatory equivalents for carbon dioxide production, (VD/VT) dead-space to tidal volume ratio, ( $\dot{V}_E/\dot{V}_{CO_2}$ ) ventilatory equivalent ratio for carbon dioxide

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