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I am submitting herewith a dissertation written by Daniel Martin entitled "Chronic Obstructive Pulmonary Disease Patients and Healthy Subjects: A Comparison of Ventilatory Patterns Used During Maximal Exercise and Predicting Maximal Oxygen Uptake from Resting Pulmonary Function Testing." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Education.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS AND HEALTHY SUBJECTS: A COMPARISON OF VENTILATORY PATTERNS USED DURING MAXIMAL EXERCISE AND PREDICTING MAXIMAL OXYGEN UPTAKE FROM RESTING PULMONARY FUNCTION TESTING

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ABSTRACT

The purposes of this study were to develop equations to predict maximal oxygen uptake from resting measures of pulmonary function testing (PFT) and to compare the ventilatory patterns used during maximal exercise in chronic obstructive pulmonary disease (COPD) patients and healthy non-smoking subjects. Eleven COPD patients (8 males and 3 females) and 8 healthy male subjects were given PFT and a graded, maximal treadmill test. As expected, the healthy subjects performed significantly better on the PFT and treadmill test. Several resting PFT measures were significantly correlated with maximal oxygen uptake expressed as $ml \cdot kg^{-1} \cdot min^{-1}$ and liters/min. Regression equations were:

$ml \cdot kg^{-1} \cdot min^{-1}$ = 5.326 + 12.17 X maximum ventilatory volume/mass (kg), r = 0.90, S.E.E. = 4.4 $ml \cdot kg^{-1} \cdot min^{-1}$

$ml \cdot kg^{-1} \cdot min^{-1}$ = 6.19 + 2.259 X peak expiratory flow (percentage of expected), r = 0.79, S.E.E. = 6.4 $ml \cdot kg^{-1} \cdot min^{-1}$

liters/min = 0.0326 + 0.2437 X peak expiratory flow (PEF), r = 0.89, S.E.E. = 0.413 liters/min

liters/min = 0.0041 + 0.8166 X carbon monoxide diffusing capacity (D_{LCO}), r = 0.83, S.E.E. = 0.507 liters/min

liters/min = -0.2282 + 0.167 X PEF + 0.038 X D_{LCO}, r = 0.93, S.E.E. = 0.34 liters/min

Four variables were used to characterize ventilatory patterns during maximal exercise, tidal volume/forced vital capacity (V_t/FVC),

maximal ventilation/MVV (Ve_{max}/MVV), frequency of breathing (F_b) and peak expired flow at rest/peak expired flow during exercise (F_{Prest}/F_{Pex}). The COPD patients' mean Ve_{max}/MVV ratio (74 $\pm$ 25%) was significantly higher than the healthy subjects, (62 $\pm$ 22%, $p < 0.03$). The healthy subjects had a greater V_t/FVC ratio (62 $\pm$ 11%) than the COPD patients (47 $\pm$ 13%, $p < 0.01$). The F_b did not differ between groups; 31.7 $\pm$ 7.8 breaths per minute for the COPD patients and 32.0 $\pm$ 4.1 breaths per minute for the healthy subjects. F_{Prest}/F_{Pex} did not differ between groups, 68 $\pm$ 30% for the COPD patients and 62 $\pm$ 22% for the healthy subjects.

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CHAPTER I

INTRODUCTION

Statement of the Problem

Rehabilitation programs for coronary artery disease patients have evolved over the past two decades to the point that exercise testing and the prescription of exercise are routinely used. Much of the early work with these patients attempted to identify factors associated with the limitations in work performance in this population, such as ventricular arrhythmias, ST-segment depression, and others. Exercise, in combination with drug therapy, was then used to increase work tolerance, using these objective signs of effort intolerance as end points.

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and death in the United States today, ranking second only to coronary artery disease as a cause of Social Security disability compensation (American Cancer Society, 1980). Approximately 23,000 deaths in 1978 were attributed to COPD. The use of exercise in the rehabilitation of COPD patients is at the same stage as the training of cardiac patients 20 years ago. There is a need to identify the basic pulmonary, metabolic and cardiovascular responses of this population to maximal, graded exercise in order to determine the factors that (1) limit performance, and (2) distinguish them from a "normal" population. This information could then be used to do

longitudinal studies on COPD patients, with the focus on how exercise modifies the pathological responses or simply postpones the onset of the pathological response.

Purposes of the Study

The purposes of this investigation were to compare the ability of resting measures of pulmonary function to predict maximal oxygen uptake and to compare the ventilatory patterns by which healthy subjects and COPD patients adapt to graded, maximal exercise.

Limitations of the Study

1. The sample sizes were relatively small, but representative of the intended populations.

2. It was not feasible in this study to obtain arterial blood samples in order to more fully evaluate the respiratory response to exercise. The use of ear oximetry provided information regarding the trend of arterial oxygenation, but the absolute magnitude of arterial saturation is open to question, as it was not possible to calibrate or verify the oximeter readings.

3. No measures of inspiratory airflow were analyzed.

CHAPTER II

REVIEW OF RELATED LITERATURE

Introduction

The relevant area of the literature may be divided into six areas:

1. Pathophysiology of COPD,
2. The respiratory system as the limiting factor in short-term work,
3. Exercise training programs for COPD patients,
4. Exercise evaluation of COPD patients,
5. Ventilatory patterns of COPD patients during maximal exercise.

Pathophysiology of COPD

Before starting the discussion of the pathophysiology of COPD, it seems appropriate to define the tests of pulmonary function that are most commonly used to evaluate the disease process. The tests used are:

1. Forced vital capacity (FVC). This is the volume of air that can be forcibly expelled from the lungs after a maximal inspiration. The FVC is expressed in liters, BTPS.
2. Forced expired volume in 1.0 seconds ($FEV_{1.0}$). This is the volume of air that is exhaled from the lungs in the first second of the FVC. The $FEV_{1.0}$ is considered to be a sensitive measure

of airway obstruction and is used as a guide to the progression of COPD in long-term follow-up studies.

3. Midvolume forced expired flow rate (FEF_{25-75}). This is the maximal flow rate achieved between 25% and 75% of the FVC. This measure is usually the first abnormality to be seen in the early stages of obstructive lung disease. The units of this measure are liters per second, BTPS.

4. Peak expired flow rate at rest (PEF_{rest}). Peak expired flow is also measured during exercise (PEF_{ex}). PEF_{ex} is obtained by averaging the peak flow (50 msec) of each breath over a full minute. PEF_{rest} and PEF_{ex} are expressed as liters per second.

5. Maximum ventilatory volume (MVV). This is the maximum volume of air that can be moved during a 12 second period. The 12 second volume is multiplied by 5 to obtain liters per minute. This test is a measure of the mechanical ability of the respiratory system to move air.

6. Carbon monoxide diffusing capacity (D_{lCO}). This test measures the volume of CO that diffuses across the gas exchange membrane, per torr of CO pressure, per unit time, and is expressed as ml/min/mm Hg, STPD. The results of this test can be decreased by anemia, or more commonly, inequality of ventilation/perfusion in the lung.

7. Total lung capacity (TLC). This is a measure of the total lung capacity as measured with the nitrogen washout technique. The nitrogen washout method tends to underestimate lung volumes in patients with obstructive changes due to the slow equilibration of the lung units.

8. Residual volume (RV). This volume is the amount of gas remaining in the lung following the FVC, and is determined by subtracting the FVC from TLC.

Classically, COPD patients with disease have been divided into two categories, emphysema or "pink puffers," and bronchitis or "blue bloaters." The resting clinical and laboratory profiles of these patients can be seen in Table 1 adapted from West (1977).

TABLE 1. Clinical Characteristics of Emphysema and Bronchitis

	Emphysema	Bronchitis
Physical findings	Dyspnea	Cough, sputum polychthemia progresses to respiratory failure
Radiology	Hyperinflation	Normal or congested lung fields
	Attenuated peripheral fields	Previous infections
Physiology	Airway obstruction	Airway obstruction
	TLC high	TLC may be normal
	increased compliance	normal compliance
	CO diffusing capacity low	normal or high
	PCO_2 normal	hypercapnia
	PO_2 usually > 65 torr	PO_2 often < 65 torr

This division of COPD patients into two distinct groups is useful for illustrative purposes, but it is frequently difficult, if not impossible to clearly separate emphysema and bronchitis in

a given patient with advanced disease. Patients with asthma can usually be differentiated from patients with emphysema or bronchitis with bronchodilators. An improvement of 15-20% in $FEV_{1.0}$ after administering bronchodilators is indicative of reversible airway obstruction, but the common factor in all of these disease categories is obstruction to airflow.

COPD is generally accompanied by four factors that decrease the efficiency of cardio-respiratory systems; an increased resistance to airflow, a lowered, flattened diaphragm, a mismatch of ventilation and perfusion, and an abnormally high pulmonary arterial pressures. The increased resistance to airflow in COPD may be caused by excessive secretions and muscle hypertrophy in the bronchial lumen as in bronchitis. Increased resistance to expiratory airflow may also be caused by dynamic compression. Dynamic compression is the result of the loss of radial tissue traction, causing air to become trapped in the small airways, despite very high intrapleural pressures. Dynamic compression is thought to be very common in COPD and is partly responsible for the high cost of ventilation in COPD patients and will be discussed later.

COPD patients often have a lower, flatter diaphragm which is in an inefficient position for generating tension, as predicted by the La Place equation. The La Place equation states that the pressure (P) across a curved surface equals the tension (T) divided by the radius (R). In mathematical terms:

$$P_{transdiaphragmatic} = T_{diaphragmatic}/R_{diaphragmatic}$$

If a constant pressure is to be generated by the diaphragm with an increasing radius, the tension the diaphragm must generate is increased. Obviously, a flatter diaphragm with an increased radius increases the tension needed to generate a given pressure. Another factor decreasing the function of the diaphragm is based on the length-tension relationship of muscle. The hyperinflation of the lungs seen in COPD results in a low diaphragmatic position and shortening of the diaphragmatic muscle fibers. This shortened resting position places the diaphragmatic muscle fibers at a poor position on the length-tension curve for generating tension. Shortened muscle fibers require a greater stimulation to generate a given tension and thus predisposes the diaphragm to fatigue. The increased resistance to airflow found with COPD, coupled with diaphragmatic mechanical and physiological problems, makes it difficult to increase ventilation during exercise.

Ventilation/perfusion mismatch is another major problem of COPD. These patients not only have difficulty increasing ventilation during exercise, but unlike healthy subjects, they do not closely match ventilation and perfusion in the lung, and thus some of the hard-gained ventilation is not efficiently used. The major causes of ventilation/perfusion mismatch in COPD include loss of lung parenchyma, shunts and gas trapping in enlarged alveoli. Ventilation/perfusion mismatch can be quantified with techniques using multiple inert gases, but this procedure is not practical in the typical clinical setting (Wagner 1977).

Abnormal pressures in the pulmonary artery of COPD patients during exercise have recently been documented by two groups of workers. Wright et al. (1983) correlated pulmonary function tests and pulmonary artery pressure preoperatively in 17 COPD patients requiring lung resection. They found that pulmonary artery pressure and cardiac output were normal at rest, but pulmonary artery pressure and pulmonary resistance increased during supine exercise. The increase in pulmonary artery pressure during exercise was positively correlated with a decrease in FEF_{25-75}. Postoperatively, histologic measures of obstructive changes in lung specimens were also positively correlated with an increase in pulmonary artery pressure during exercise. The authors hypothesized that gas trapping in the lungs may have led to the increased vascular resistance in the lung.

Light and co-workers (1984) analyzed the relationship between cardiac output and oxygen consumption at rest and during exercise in 26 patients with severe COPD. Pulmonary artery wedge pressure was normal at rest, (mean $\pm$ S.D.) 22.5 $\pm$ 10.1 mm. Hg, and increased abnormally to 45.5 $\pm$ 18.9 mm. Hg, during maximal exercise. These authors found the quantitative relationship between cardiac output and oxygen consumption to be within normal limits, but the absolute magnitude of maximal cardiac output and maximal oxygen consumption to be very low, 8.0 1/min and 0.81 1/min, respectively.

The increase in pulmonary artery wedge pressures seen in COPD patients is probably causally related to the high incidence of right ventricular hypertrophy and heart failure seen in these patients.

The high wedge pressure may also limit the heart's ability to increase cardiac output, further aggravating ventilation/perfusion equality to result in hypoxemia.

In summary, COPD is accompanied by four major factors that decrease the function of the integrated respiratory and circulatory system; increased resistance to airflow, a low, flattened diaphragm, ventilation perfusion mismatch and abnormally high pulmonary artery pressures during exercise. The lower, flatter position of the diaphragm places this muscle at a disadvantage for overcoming the increased resistance to ventilation, and the air that does reach the gas exchange regions of the lung is not efficiently used due to ventilation/perfusion mismatch. The high pulmonary artery wedge pressures can lead to right heart failure and decreased maximal cardiac output.

Two secondary factors contribute to the sub-optimal exercise performance of COPD patients, inactivity and cachecia. Many COPD patients become very inactive as a result of shortness of breath during daily activities. As these individuals become short of breath, they limit their physical activities to decrease the feeling of dysnpnea, and become further deconditioned. Patients with advanced COPD are often underweight, and this may contribute to diaphragmatic fatigue. Kelsen, et al. (1985) found that placing rats on a hypocaloric diet, which resulted in a 25% decrease in body weight, reduced the diaphragmatic mass by about 33%.

The Respiratory System as the Limiting Factor in Short-Term Work

It is generally accepted that ventilation does not limit maximal performance in healthy subjects at sea level, although highly trained athletes have been shown to decrease arterial hemoglobin saturation during very high level exercise (Dempsey 1980 and Rowell 1964). Pulmonary function has been implicated in limiting maximal performance in COPD patients (Jones 1971 and Brown 1985a). In a recent review, Bye et al. (1983) listed four aspects of pulmonary function that may contribute to performance limits in healthy subjects and patients with COPD. These factors are:

1. Derangements of pulmonary gas exchange,
2. Mechanics of breathing,
3. Energetics of the respiratory muscle,
4. Fatigue of the respiratory muscles.

Arterial partial pressures of oxygen and carbon dioxide are the most elemental means of evaluating the adequacy of pulmonary gas exchange. The respiratory system has adequate reserves such that decreases in P_aO_2 or increases in P_aCO_2 at rest are seen only in advanced cases of lung disease. However, P_aO_2 does fall normally with advancing age. An 80 year old with a P_aO_2 of 75-80 mm Hg is not hypoxemic, while this finding in a resting 20 year old would be cause for considerable concern. CO_2 is about 20 times more soluble in body fluids than O_2, and elevations in P_aCO_2 are usually seen only in drug or trauma induced hypoventilation and severe cases of COPD.

Exercise has been shown to decrease P_aO_2 in some COPD patients (Owens 1984 and Raffestein 1982) and highly trained runners during maximal exercise (Dempsey 1982), but the average healthy subject is unlikely to experience significant decreases in P_aO_2 during maximal exercise at sea level.

Factors affecting the P_aO_2 can be subdivided into extra-pulmonary and intra-pulmonary factors. Decreased F_1O_2 is the most likely mechanism of extra-pulmonary reduction in F_1O_2. Decreasing the F_1O_2 in the laboratory, or at altitude can result in decreases in P_aO_2 (Torre-Bueno 1985). Alveolar hypoventilation is another extra-pulmonary cause of a decreased P_aO_2, but is rarely seen in healthy subjects.

Alveolar ventilation/perfusion mismatching, diffusion disequilibrium and shunts are the primary intrapulmonary factors affecting P_aO_2. Intrapulmonary shunts are a potent cause of arterial hypoxemia, but shunted blood flow accounts for only about 3% of cardiac output in healthy subjects (West 1979). Alveolar ventilation/perfusion is a major cause of arterial hypoxemia in COPD patients (West 1979), but this technique is not feasible for routine clinical use.

Diffusion disequilibrium is thought to be the mechanism of hypoxemia in highly trained athletes. Dempsey (1982) examined 20 highly trained distance runners working at > 85% (4 to 5 liters/min) of Vo_{2max} and found physiologically significant decreases in P_aO_2 during maximal exercise. The P_aO_2 decreases ranged from 10 to 40 mm Hg, with corresponding saturation levels falling to the low

90's to mid 80's. The decreases in P_aO_2 were attributed to three causes:

1. very low (less than 2 ml O_2/ 100 ml of blood) levels of oxygen in mixed venous blood,

2. inadequate time for equilibration of red blood cells with alveolar PO_2 in the lung in the presence of the large cardiac outputs (approximately 30-35 liters per minute) needed to maintain these oxygen consumptions; and

3. a relative hypoventilation for the metabolic load.

The decreases in arterial saturation were usually not seen in athletes that maintained PAO_2 above 110 mm Hg.

Mechanics of Breathing

COPD is associated with changes in the airway resistance and diaphragmatic function that have been reviewed in the pathophysiology section and will not be covered here. These factors play a role in the mechanics of breathing in COPD patients that should not be overlooked.

During maximal exercise, COPD patients generally use a greater percentage of their maximal ventilatory volume than healthy subjects. This has been interpreted as a pulmonary limitation to performance (Jones 1971 and Brown 1985a). Healthy subjects, on the other hand, rarely use more than 70% of MVV during maximal exercise, and theoretically have substantial ventilatory reserves remaining. Jones (1984) has criticized the MVV as a measure of exercise ventilatory

capacity. The MVV is usually performed at higher lung volumes than exercise ventilation, and thus greater expiratory flow rates are achieved. The greater lung volumes increase the diameter of the airways and reduce resistance to airflow.

The flow-volume loop is proposed by Jones (1984) as an alternate method of estimating the fractional utilization of breathing capacity. (The flow-volume loop is a record of volume and flow during the FVC.) Achieving flow rates during exercise that equal those of the resting flow-volume loop would indicate that the maximal flow rates had been achieved, and further increases in ventilation could only be realized by increasing the frequency of breathing. Grimby and co-workers in 1971 showed that highly trained athletes did reach maximal expiratory flow rates during exercise that equalled peak flow rates achieved during flow-volume loops, and this may indicate that these athletes did reach maximal ventilatory levels during maximal exercise.

Energetics of Breathing

The work of breathing can be divided into three components lung compliance, lung and chest wall tissue resistance and airway resistance (Guyton 1981). At rest, the major portion of the work of breathing is spent overcoming the lung's resistance to expansion. Tissue resistance is the smallest factor in the work of breathing, but can be increased to very high levels in restrictive diseases such as scoliosis. Airway resistance to airflow normally comprises a small percentage of the work of breathing during rest in healthy

individuals, but plays a larger role during exercise when ventilation is increased. Airway resistance is increased in COPD at all times. Reductions in the radius of the bronchi due to muscle hypertrophy and mucous are often found in COPD. All other factors held constant, flow through a tube is proportional to the radius raised to the fourth power, so a 10% reduction in the radius of a tube will reduce flow by about 35%.

The oxygen cost of breathing in COPD patients is greater at rest and during exercise than in healthy subjects. Field (1982) investigated the cost of breathing in 13 acutely ill COPD patients during "weaning" from mechanical ventilation. The cost of breathing was measured as the difference between oxygen consumption during spontaneous breathing minus the oxygen consumption during mechanical ventilation. Oxygen consumption averaged 312 ml/min during spontaneous respiration and 246 during mechanical ventilation. The mean difference, 78 ml/min represented almost 31% of the resting oxygen consumption during mechanical ventilation. In contrast, the oxygen cost of breathing at rest in healthy subjects is estimated to be only 3-5% of metabolism (Guyton 1981). Levision and Cherniak (1968) found the oxygen cost of breathing at rest to be 1.9 and 6.3 ml/liter in healthy subjects and COPD subjects, respectively. During exercise, the oxygen cost of breathing increased to 4.2 ml O_2/liter for healthy subjects and 9.3 ml O_2/liter for COPD patients.

At high ventilations it is possible that the respiratory muscles, especially the diaphragm, might "steal" oxygen from the skeletal muscle.

Robertson et al. (1977) reported diaphragmatic blood flow of 200 ml per 100 g of muscle tissue during resistive breathing. Bye (1983) estimated that the respiratory muscle mass in a 70 kg man equals 4 kg. Assuming an a-VO_2 difference of 15 ml/100 ml with an 8 liter/minute flow (4 kg of resp muscle X 2 liters/kg of resp muscle/min = 8 liters/min) to the respiratory muscles, the result is an oxygen consumption of 1.2 liter/minute, or 25-33% of the maximal oxygen consumption in a young man. The very high blood flow to the respiratory muscles may reduce the blood flow to the working skeletal muscle and limit performance.

Respiratory Muscle Fatigue

Muscle fatigue can be defined as the inability to generate a constant tension, despite a constant stimulation. Respiratory muscle fatigue is a concept that is receiving increasing attention from investigators. Despite its high aerobic capacity, the diaphragm can apparently become fatigued. Two factors seem to predispose the diaphragm to fatigue; generating more than 40% maximal transdiaphragmatic pressure, and breathing at very high lung volumes. Roussos (1977) found that subjects could maintain ventilation for indefinite periods of time if the diaphragm was generating less than 40% of its maximal transdiaphragmatic pressure. Once the 40% figure was exceeded, the performance time decreased rapidly. Diaphragmatic fatigue while breathing at high lung volumes is probably related to the increase of the diaphragmatic radius and shortening of the diaphragmatic muscle

fibers, which places the muscle at a disadvantage for generating tension, as discussed earlier.

An additional factor that may limit the work capacity of the diaphragm is hypercapnia. Schnader and co-workers (1985) showed that acute hypercapnia (PCO_2 > 46 torr) resulted in a decreased diaphragmatic force production in an in vivo dog preparation. Hypercapnia of this magnitude is frequently seen in COPD, particularly in those patients with bronchitis, and may contribute to diaphragmatic fatigue and dyspnea.

There is some evidence that respiratory muscle fatigue does occur in healthy subjects following heavy exercise. Shepard (1967) found the MVV reduced after 20 minutes of exercise at 80% of VO_{2max}, but not after 5 minutes of similar intensity work. Locke et al. (1982) found maximal inspiratory pressure and MVV to be reduced following marathon running in four runners. Investigations comparing respiratory muscle function before and after acute exercise bouts have not been completed with COPD patients.

Training Studies in COPD Patients

Several workers have shown that endurance and/or VO_{2max} may be improved in COPD patients, but the results are not as consistent as those found in studies using elderly subjects, or patients with coronary artery disease. Many of the early studies examining exercise training with COPD patients were poorly designed; few control groups were used, the intensity of training was often not quantified, and

the training loads were usually not increased during the course of the training.

Pierce et al. (1964) published one of the first studies examining the trainability of COPD patients. These workers trained 9 COPD patients daily on a treadmill for 2.5 minutes, 5-10 times per day for 8 $\pm$ 7.1 weeks, (range 2-20 weeks). During the course of training, the speed of the treadmill was increased as the patients were able to tolerate increased speed. Following training, the oxygen cost of walking at a given submaximal workload was reduced by about 25% and the VO_{2max} was increased by about 30%, from 1090 ml/min to 1336 ml/min. While this study did not employ an optimally quantified training program, it was one of the first attempts at training COPD patients. These authors concluded that COPD patients were able to improve submaximal efficiency and maximal performance with training.

Sergysels, DeCoster and Denolin (1979) studied the effect of 6 months of training on 20 COPD patients. One-half of the group performed "low frequency breathing with high tidal volume and adequate abdominal motion," while the remaining 10 subjects added cycling for 25 minutes at 75% of the previously determined maximal loads. No mention was made of any increases in training loads over time in the cycle training program. Following training, the breathing exercise group demonstrated a decrease in arterial PCO_2 and significant increases in TLC, VC, $D1_{CO}$. The breathing plus cycling training group increased VO_{2max} by 13.6%, $p < 0.05$. This study is one of the few works to show any increases in the resting measures of pulmonary function.

Nicholas and co-workers (1970) studied 15 COPD patients during a 3 month control period and during 6 months of exercise training. The control period served to insure that the patients were in a stable phase of their disease and to allow them to become skilled at walking on a treadmill. During the control period, patients reported to the training site once per week and walked on the treadmill at very low speeds. Training was conducted three times per week, with three walking bouts per session. The treadmill settings were 1.7 mph, 0% grade, 1.7 mph, 10% grade or 3.0 mph, 10% grade. The unique protocol for the three training walks each day is given below:

> The first walk was at the lowest stress which the subject could not sustain for 10 minutes, but could sustain for at least one minute. The second walk was for a maximum of 10 minutes at the next lower stress, and the third walk was at the previous higher stress.

Three subjects required 12 months to complete the equivalent of 9 months of training. During the course of the training seven patients dropped out of training. Four of the remaining patients improved VO_{2max}, while four did not. The mean VO_{2max}, before and after "training" were not given.

DeCoster et al. (1979) trained 20 COPD patients, divided into 2 groups, for 6 months. One group performed breathing exercises 5 times per week for 45 minutes, while the remaining patients added 25 minutes of bike training 3 times weekly. After six months of training, the breathing exercise only group had improved $D1_{CO}$, but not VO_{2max}. The bike plus breathing group improved VO_{2max} by

14%. The authors concluded that endurance training plus inspiratory muscle training were more effective at increasing function capacity than breathing exercises alone. The small number of subjects and unusual training program make this study difficult to evaluate.

Belman and Mittman (1980) evaluated the effects of isocapnic inspiratory muscle training for 15 minutes, twice a day for 6 weeks on submaximal performance time, 12 minute walking distance and maximal exercise ventilation in 9 COPD patients. Following training, endurance time at approximately 66% of pretraining, maximal work rate improved from 7.0 to 10.8 minutes ($p < 0.01$), maximal distance walked in 12 minutes increased from 1058 to 1188 meters ($p < 0.01$) and maximal exercise ventilation increased from 32 to 36 liters/min ($p < 0.01$). Unfortunately, VO_{2max} was not reported, but maximal load (66 $\pm$ 19 watts) achieved during cycling was not significantly increased after training (75 $\pm$ 26 watts).

Pardy et al. (1981) compared the efficacy of ventilatory muscle training with endurance training in 17 patients as measured by distance walked in 12 minutes, performance time at 60% of maximal oxygen consumption, and VO_{2max}. Patients trained for 30 minutes, 3 times per week for 2 months on an inspiratory muscle trainer, or on treadmill, steps, bicycle and with light weights. After training for 2 months, the inspiratory trainers had significant increases in 12 minute walk distance and performance time at 60% of maximal oxygen consumption, while the endurance training group did not increase after the control period. VO_{2max} was not significantly different

in either group after training. The authors concluded that inspiratory muscle training at home was a more effective means of increasing functional capacity than this particular in-hospital directed endurance training program.

There are several possible problems with this study that may explain the lack of significant training effects in the endurance trainers. Training was primarily conducted on a cycle ergometer, while testing was conducted on a treadmill. The resistance on the cycle ergometers was not increased during training, and the two groups trained for a different length of time each day. The training program in this study was so poorly designed and controlled, it is difficult to understand how the authors could state that one program was superior to the other.

Belman and Kendregan (1981) evaluated the effects of exercise training on enzymatic markers of aerobic and anaerobic activity in muscle, an incremental maximal exercise test, and a submaximal performance test at two-thirds to three-quarters of the pretraining maximum workload. The enzymes analyzed included citrate synthase, as an indicator of the citric acid cycle; 3-β hydroxylase co-enzyme A, as an indicator of Beta oxidation; and pyruvate kinase, as an indicator of anaerobic enzyme activity. Seven patients trained 4 times per week, 2 20-minute sessions per day, for 6 weeks with cycle ergometers. Training intensity was "set at approximately one-third the maximum reached in the incremental test." This was increased as rapidly as possible to a load that could be tolerated for the full 20 minutes.

Initial training loads tolerated for 20 minutes on the cycle ergometer were 26 watts and after 6 weeks of training improved to approximately 42 watts. After training, endurance time at two-thirds to three-fourths of the initial maximal workload improved significantly from approximately 7 to 15 minutes. Endurance times are approximate; the tabular data were not included in the paper and had to be estimated from a graph. None of the enzymatic markers of aerobic activity increased activity after training. The authors concluded that training did enable COPD patients to improve submaximal performance time, but the intensity of training was apparently too low to induce increases in the enzymatic activity, as documented with healthy subjects. The COPD patients did not increase the activity of pyruvic kinase, but this was not unexpected, as healthy subjects have also been shown not to increase the activity of this enzyme in response to endurance training.

The most significant problem with this study is the very low intensity of training. Training was initiated at approximately one-third of maximal workload and was then moved to a load that could be tolerated for 20 minutes. There is no way of knowing the actual percentage of maximal functional capacity at which these patients were trained; it is possible that training was conducted at intensities below the threshold required to elicit enzymatic changes.

Booker (1984) evaluated the effects of a 12 month program of stair climbing on distance covered in 6 minutes of walking (6MWD). One hundred and two patients were allocated to three groups; control,

exercise and physical therapy. The control group reported to the laboratory once a month for pulmonary function testing and 6MWD. The exercise group followed a step training program developed by McGavin et al. (1977), which consisted of step climbing. Training load was increased by increasing the number of steps climbed and the duration of climbing. Training during the first 2 weeks consisted of climbing 5 steps for 2 minutes and increased to climbing 15 steps for 15 minutes by week 12. The physical therapy group was taught diaphragmatic breathing exercise, breathing control drills and relaxation techniques in addition to the stair training program. Patients were assessed after 3, 6 and 12 months of training by an observer who was not aware of the treatment the patient had received. After training, there were no significant increases in the 6MWD in any of the three groups.

This study has two shortcomings, training and testing were conducted on different types of equipment, and the intensity of training was not quantified. Training was done on steps, and post-training evaluation was conducted on level walking. These two activities utilize different muscle groups. It is possible that the patients may have demonstrated improvement if testing had been conducted on the same apparatus as training. The intensity of training appears to have been poorly controlled, since there were no specific criteria used to determine when increases in absolute workloads would be made.

O'Hara et al. (1984) studied the effects of a 6 week, moderate weight training program on the exercise responses of 14 COPD patients. Seven patients were given five weight lifting exercises, wrist curls, arm curls, partial leg squats, calf raises and supine dumbell presses. The initial weight of the dumbell was 4.3 $\pm$ 0.9 kg and was increased by 1.2 $\pm$ 0.5 kg every week, resulting in a final load of 10.4 $\pm$ 2.6 kg. Training was conducted at home on a daily basis. The remaining seven patients formed the control group and were given a light backpack to wear while walking a few minutes each day. Patients were evaluated on the distance covered during a 12 minute walk and with a maximal bicycle ergometer test. Following training, the control patients did not increase distance walked during the 12 minute test, maximal ventilation, or maximal heart rate. The weight trainers significantly improved 12 minute walking distance by 16%, decreased exercise ventilation at a given submaximal workload by 18% and increased maximal heart rate by 10%.

This study was conducted because the authors noted that patients near normal body weight did better than patients who were significantly underweight. The weight training was an attempt to increase muscular strength in these patients and improve functional ability. This study presents a promising, new approach to the training of COPD patients.

Chen et al. (1985) investigated the effects of inspiratory muscle training in COPD patients undergoing exercise rehabilitation training. Six control patients were given traditional exercise training programs, and seven patients were given inspiratory training

exercises in addition to the standard training program. The standard exercise group trained for 20 minutes with "moderate" ergometer cycling, 3 times per week. Further details regarding the intensity of the cycle exercise training were not given. The inspiratory muscle training consisted of inspiring through 1-inch plexiglas rods with varying levels of resistance. The diameter of the holes ranged from 2.5 to 6 mm, corresponding to resistance of 45 to 5 cm of H_2O/1/sec. Training was conducted for 15 minutes, twice a day for 4 weeks. The initial level of inspiratory resistance was set to yield a mouth pressure of 60% of the previously determined maximal sustainable inspiratory mouth pressure. The standard exercise rehabilitation group trained on a similar sham trainer with an inspiratory orifice of 10 mm. All post-training evaluations were conducted in a double blind manner. These authors found inspiratory muscle training improved endurance time at 60% of maximum sustainable inspiratory pressure in the inspiratory trainers, but did not improve exercise performance as measured by submaximal endurance performance or maximal exercise capacity. The control, or standard training group, did not improve any measure of exercise performance. The authors concluded that inspiratory muscle training improved submaximal inspiratory muscle endurance, but did not improve submaximal or maximal exercise performance.

This study is among the few to find inspiratory muscle training ineffective at increasing the exercise performance of COPD patients. The fact that treatment was double-blind raises questions about the

unintentional bias influencing the performance in other studies. The exercise training aspects of this study were treated very briefly. Details of the intensity and volume of training were not included in the paper, and this may explain the lack of increases in the exercise training group.

A great deal of work remains to be done to determine the optimal training program for COPD patients, if one exists. A major problem encountered when comparing training studies involving COPD patients is the lack of a common measure of exercise training intensity. Healthy subjects and cardiac patients are usually trained at 60-80% of VO_{2max}, but many authors have not included data indicating the intensity of exercise training. The COPD patients are often not carefully stratified according to severity of disease. It is possible that patients below some level of functioning are not able to train at intensities sufficient to elicit the typical training effects. One topic that would certainly be worth investigating would be a training study involving four groups of equally impaired patients; control, inspiratory muscle training, endurance training and a group combining both types of training. However, before such a study could be started, more information is needed to define the optimal training program for each modality to insure that valid comparisons are being made between training modalities.

Exercise in Evaluation COPD

Jones and co-workers (1971) evaluated the ability of FVC, $FEV_{1.0}$, DL_{CO} to predict exercise tolerance in 50 patients with COPD.

Forty-eight of the 50 patients had been cigarette smokers, and 28 were still smoking. Unfortunately, no healthy subjects were included in the analysis. Mean age was 60.3 $\pm$ 7.6 (range 43 to 73 years), and all patients were in a stable phase of their disease. The strongest correlation between pulmonary function and maximal workload was with $FEV_{1.0}$ ($r = 0.621$, $p < 0.001$), followed by FVC ($r = 0.561$, $p < 0.001$), DL_{CO} ($r = 0.539$, $p < 0.001$), airway resistance ($r = -0.416$, $p < 0.01$) and age ($r = -0.341$, $p < 0.05$). Multiple regression predicting maximal workload achieved during cycle testing via resting pulmonary function was:

$$KGM_{max} = 563 - (5.4 \text{ X age}) + (142 \text{ X } FEV_{1.0}) + (7.5 \text{ X } D_{Lco})$$

($r = 0.73$; SEE = 122 KGM)

This study demonstrates that exercise performance increases with increases in pulmonary function in COPD patients; but did not include healthy subjects.

McGavin et al. (1976) examined the relationship between distance covered during a 12 minute walk, pulmonary function, and VO_{2max} in 29 patients with chronic bronchitis. Patients were given a practice attempt at the 12 minute walk, and the second effort was used in data analysis. The authors found $FEV_{1.0}$ was moderately correlated with VO_{2max} ($r = 0.65$, $p < 0.01$), while the correlation between 12 minute walking distance and VO_{2max} ($r = 0.52$, $p < 0.01$) was weaker. The authors concluded that "although $FEV_{1.0}$ correlates well with VO_{2max}, it does not predict effort intolerance in tests requiring more prolonged submaximal effort."

Two groups of investigators have examined the effects of helium-oxygen mixtures on maximal ventilation and performance in COPD patients. Raimondi (1970) found that a helium-oxygen mixture increased maximal ventilation, but did not enhance maximal power output. Bradley (1980) found that a 79% helium-21% oxygen mixture did not increase maximal ventilation or power output, compared to the same oxygen concentration in nitrogen. Both of these studies used small groups of subjects, and there was apparently no attempt to match the patients on severity of disease.

COPD patients have been shown to have increased time constants for increases in oxygen consumption, VCO_2, heart rate and ventilation. Nery and co-workers (1982) compared oxygen uptake kinetics in 9 COPD patients and 6 normal, untrained men at 50% of VO_{2max}. Testing was conducted on an electrically braked cycle ergometer, at "subanaerobic threshold" levels of exercise. However, the anaerobic threshold could not be determined in two of the COPD subjects, due to limitations in the ventilatory response to exercise. The patients had a mean $FEV_{1.0}$ of 1.1 $\pm$ 0.33 liters, and were in a stable phase of their disease. The rates of increase during phase 1 of the rise in metabolic and ventilatory parameters for the patients and healthy subjects, respectively were VO_2 = 0.10 $\pm$ 1.05 vs 0.24 $\pm$ 0.04 1/min, VCO_2 = 0.10 $\pm$ 0.03 vs 0.22 $\pm$ 0.03 1/min and VE = 3.4 $\pm$ 0.89 vs 6.8 $\pm$ 1.05 1/min. The time constants for all parameters were significantly shorter in the healthy subjects. The authors observed that the slowed time constants of the COPD patients were more closely related to a slowed

cardiovascular response, rather than indices of respiratory function. Unfortunately, the authors did not elaborate on this observation or present any quantitative argument to support this statement.

In 1984, Brown and co-workers examined the effects of added deadspace during maximal exercise on VO_{2max}, ventilation and blood gases in 22 COPD patients and 9 healthy subjects. The COPD patients were severely impaired as evidenced by their $FEV_{1.0}$, which averaged 0.96 ± 0.41 liters. Deadspace was placed between the mouthpiece and breathing valve and was adjusted according to the patient's $FEV_{1.0}$. If $FEV_{1.0}$ was less than 0.8 liter, 250 ml was added, while patients with a $FEV_{1.0}$ greater than 0.8 liter had 500 ml of deadspace added. The added deadspace for the healthy subjects was 1000 ml. The healthy subjects significantly increased maximal ventilation by 25.3 liters/min (22%) with the added deadspace, and VO_{2max} was unchanged. The COPD patients also increased maximal ventilation significantly by 12%, but VO_{2max} decreased by 12%. The increased ventilation in both groups was achieved primarily through increases in tidal volume, rather than frequency. The authors concluded the healthy subjects had enough ventilatory reserve to maintain adequate alveolar ventilation despite the added deadspace, while the COPD patients lacked sufficient ventilatory reserve to increase ventilation with added deadspace to achieve control VO_{2max}. These results support the premise that the maximal exercise performance of COPD patients, but not healthy subjects, is limited by ventilatory mechanics.

In 1984, Owens and co-workers evaluated the sensitivity and specificity of resting measures of pulmonary function testing to predict arterial desaturation during treadmill exercise in 48 COPD patients. Specificity is defined as the incidence of true negative tests divided by the sum of false positive and true negative tests. Sensitivity is defined as the incidence of true positive tests divided by the sum of true positive plus the false negatives tests. Only two pulmonary function tests were of value in predicting which patients would experience decreases in arterial oxygen saturation, a $FEV_{1.0}$ and D_{LCO} below 55% of predicted. A D_{LCO} above 55% was 100% specific in excluding desaturation, compared with an 82% specificity for an $FEV_{1.0}$ above 55% of predicted. The sensitivity of a D_{LCO} above 55% of predicted was 68%, compared with 46% for an $FEV_{1.0}$ of 55% of predicted. The incidence of arterial desaturation increased dramatically in those patients with a D_{LCO} of less than 55%. The authors concluded that patients with a D_{LCO} below 55% of predicted would probably benefit from supplemental oxygen during exercise training.

Brown (1985a) examined the reproducibility of maximal oxygen consumption in 11 COPD patients on three occasions. Patients were given two maximal tests on the same day, separated by 60 minutes. A third maximal test was administered on the following day. Mean oxygen consumptions during testing on day 1 were 1.31 ± 0.26 and 1.31 ± 0.28 1/min. Maximal oxygen consumption the following day was 1.31 ± 0.29 1/min. None of these values were significantly

different from each other. Similar agreement was found when ventilation, tidal volume, frequency of breathing, heart rate and respiratory exchange ratio were compared. It is apparent that results of maximal testing with COPD patients are as reproducible as testing of healthy subjects (Astrand 1977).

The effects of a 920 Kcal carbohydrate liquid meal on the maximal exercise response of COPD patients was evaluated by Brown and coworkers (1985b). The authors hypothesized that increased ventilation resulting from the carbohydrate meal might decrease exercise tolerance. This large carbohydrate meal decreased the COPD patient's maximal power output on a cycle ergometer from 86 to 76 watts, $p < 0.001$. Ventilation and VCO_2 at a given submaximal power output were increased in the COPD patients with the carbohydrate load, but ventilation at exhaustion was not different, 47.6 vs 46.8 1/min, $p > 0.05$. The carbohydrate load did not lower maximal power output, VO_{2max}, VCO_{2max}, or maximal ventilation in the six healthy subjects. The authors attributed the significant decrease in maximal power output in the patient group to an increased ventilation and VCO_2 at equivalent power outputs, compared to control conditions; however, the authors did not address a discrepancy in the results. Unlike the COPD patients, the healthy subjects were able to maintain maximal power output with the carbohydrate load, despite not increasing maximal ventilation. Ventilation for the control subjects was 137 ± 29 1/min for fasting and 129 ± 16 1/min for the carbohydrate load, $p > 0.05$.

Overall, the results of studies using resting measures of pulmonary function have found that exercise performance decreases as pulmonary function decreases, but the relationship is far from perfect. Studies that have placed additional stress on the respiratory reserves during maximal exercise, such as added deadspace and carbohydrate meals, have resulted in reduced exercise performance in COPD patients, while healthy subjects generally do not experience any decreased performance with the added stress.

Ventilatory Patterns in Healthy Subjects and COPD Patients

There has been relatively little work comparing ventilatory patterns between average subjects and athletes and even less work comparing healthy adults and COPD patients. Folinsbee and co-workers (1983) compared the ventilatory patterns of age-matched (mean = 21) sedentary subjects with elite cyclists during cycling tests. There were no significant differences between the groups in physical characteristics, but as expected, the trained cyclists had much greater maximal O_2 consumption, CO_2 productions and ventilations. The cyclists used a higher percentage (89 $\pm$ 7%) of their 15 second MVV than the sedentary group (71 $\pm$ 10%). The ratio of maximal tidal volume divided by FVC was similar in both groups, 47% $\pm$ 4% for the cyclists and 49% $\pm$ 6% for the untrained subjects. The greater ventilation of the trained cyclists was achieved by a higher frequency of breathing, 63 $\pm$ 7 vs. 49 $\pm$ 6, with corresponding decreases in the inspiratory

and expiratory flow times. The authors concluded that the trained cyclists and sedentary subjects utilized essentially the same ventilatory patterns to adapt to maximal exercise. The major difference was that the trained riders apparently had a briefer, more forceful contraction of the respiratory muscles that resulted in shorther durations of inspiration and expiration, rather than greater tidal volumes.

Mahler and co-workers (1982) reported on the ventilatory patterns utilized during maximal exercise in 20 experienced runners and 20 sedentary controls. The runners' maximal exercise ventilation was 86% of MVV, while the controls used 69.5%. The maximal breathing frequency and other parameters of ventilatory patterns were not reported.

Nery (1982) reported the ratio of maximal exercise V_E divided by MVV in six COPD patients and nine healthy controls. The COPD patients used 93% of MVV during maximal exercise, while the healthy subjects used 57%.

Brown (1984) reported the ventilatory patterns of COPD patients used during maximal exercise. These patients achieved maximal exercise ventilation that equalled 73% of the 10 second MVV. The ratio of maximal tidal volume divided by FVC was 45%, and maximal breathing frequency was 30.1 $\pm$ 6.4 breaths/minute. Corresponding data for the healthy control subjects were not reported. Minh et al. (1979) reported similar (31.4 $\pm$ 7.4 breaths per minute) maximal breathing frequency in 17 COPD patients undergoing treadmill testing.

Yerg and co-workers (1985) compared ventilatory patterns utilized by Master athletes (mean age = 63 years) and age-matched sedentary controls during maximal exercise. The Master athletes utilized a significantly greater fraction of their MVV during maximal exercise than the untrained controls, 70 $\pm$ 11% vs 55 $\pm$ 15%. After 1 year of training that resulted in a 23% increase in maximal oxygen consumption, the former sedentary subjects increased the fractional utilization of MVV to 69 $\pm$ 14% during maximal exercise.

The literature indicates that trained, healthy subjects and COPD patients tend to use a greater percentage of MVV during maximal exercise than untrained, healthy subjects. Maximal breathing frequency seems to be negatively related to age, but this could be a result of older subjects not exerting themselves to the same degree as younger subjects. There is little additional information documenting the other aspects of the ventilatory patterns (V_t/FVC, peak $flow_{rest}$/ peak $flow_{exercise}$) used by COPD patients and age-matched healthy subjects in their adaptation to graded maximal exercise.

CHAPTER III

METHODS

Purpose

The purposes of this investigation were to evaluate the ability of resting measures of pulmonary function to predict maximal exercise tolerance and to compare the ventilatory patterns used by COPD patients with age-matched healthy control subjects during graded, maximal exercise.

Subjects

Eight healthy subjects were recruited via personal contact and information sheets circulated in the University community. Criteria for inclusion into the control group included:

1. Fifty-five years of age or older,
2. Sedentary, i.e., not engaged in any systematic exercise program in the past six months,
3. No history of cardiovascular disease or pulmonary disease,
4. Not under a physician's care for any medical problem,
5. No exposure to substances known to impair respiratory function,
6. No lower respiratory tract infections in the past three months,
7. Life-long non-smoker,
8. No orthopedic, neurological or medical conditions that might limit maximal exercise.

Eleven COPD patients were recruited from the rolls of physicians specializing in pulmonary medicine. Criteria for inclusion into the patient group included:

1. A diagnosis of COPD, ($FEV_{1.0}$ < 70% of predicted),
2. No lower respiratory tract infections in the past three months,
3. No orthopedic, neurological or medical conditions that might limit maximal exercise,
4. No history of myocardial disease.

Informed Consent

Informed consent was obtained from each subject after explaining the testing procedures, risks involved and potential benefits. A copy of the informed consent document is included in the Appendix A.

Pulmonary Function Testing

Pulmonary function testing (PFT) was conducted in the Respiratory Therapy Department at Fort Sanders Hospital on a Gould automated pulmonary function testing device. The pulmonary function testing equipment was calibrated prior to each test. All subjects were given several practice attempts; two valid attempts were recorded and the highest value was used. All measurements were made with the subject seated. Measures of pulmonary function included forced vital capacity (FVC), forced expired volume in one second ($FEV_{1.0}$), mid-range forced expired flow (FEF_{25-75}), peak expired flow (F_{pe}) and maximum voluntary ventilation (MVV). Total lung volume was measured with the nitrogen

washout method. Single breath carbon monoxide diffusing capacity (D_{LCO}) was measured after the method of Cotes (1965). At least 30 minutes separated repeat measurements of D_{LCO}. The intermountain (American Thoracic Society 1959) standards were used to predict the percentage of expected values for all PFT variables. Data are expressed as the mean $\pm$ the standard deviation. Variable names followed by the "%" sign represent the expected of normal for the variable.

Treadmill Testing

Following PFT, subjects were given a 10 minute accomodation period of walking on the treadmill at 1.0 to 2.0 mph, 0% grade. Treadmill testing was conducted within one week. The treadmill protocols utilized two minute stages and progressed as shown in Tables 2 and 3. Different protocols were used for the healthy subjects and the patients in an attempt to equalize test durations. All treadmill testing was maximal and was continued until the subject indicated an inability to continue exercising, or the appearance of symptoms indicating the test should be terminated, which included chest pain compatible with angina pectoris, ST segment depression equaling 0.1 Mv or more, more than 6 unifocal premature ventricular contractions per minute, multifocal premature ventricular contractions, three or more consecutive premature ventricular contractions, falling systolic blood pressure (a fall of 20 mm Hg persisting over 2 minutes) and diastolic blood pressure increasing more than 20 mm Hg over the

TABLE 2. Treadmill Testing Protocol for COPD Patients

Speed (mph)	Per Cent Grade	Elapsed Time	METS
1.0	0	2	1.8
1.5	0	4	2.2
2.0	0	6	2.5
2.0	2	8	3.1
2.0	4	10	3.6
2.0	6	12	4.2
2.0	8	14	4.8
2.0	10	16	5.3
2.0	12	18	5.9
2.0	14	20	6.4

TABLE 3. Treadmill Testing Protocol for Healthy Subjects

Speed (mph)	Per Cent Grade	Elapsed Time	METS
2.0	0	2	2.0
2.0	3.5	4	3.0
2.0	7.0	6	4.0
2.0	10.5	8	5.0
2.0	14.0	10	6.0
2.0	17.5	12	7.0
3.0	12.5	14	8.0
3.0	15.0	16	9.0
3.0	17.5	18	10.0
3.0	20.0	20	11.0

standing resting value. Subjects were observed for eight minutes following exercise while blood pressures and electrocardiograms were recorded every two minutes. Following the 8 minute exercise observation period, subjects were required to remain in the testing area for approximately 20 additional minutes for observation.

Physiological Parameters Measured During Exercise

The subject's electrocardiogram was monitored with the standard 12 lead system prior to testing and every 2 minutes during the tests with a Marquette ECG. Leads II, V_2 and V_6 were monitored during the test on an oscilloscope to detect potential arrhythmias. Heart rate was obtained by conversion of the analog rate signal from the Marquette electrocardiograph to a digital signal by the Beckman Metabolic Cart at 50 Hz and averaged over 1 minute intervals. Age-adjusted maximal heart rate was calculated according to the formula of Lange-Anderson (1971):

Maximum heart rate = 210-0.65 X age (years)

Blood pressure was measured in the standing position prior to testing, and once every two minutes during testing with a sphygmomanometer placed on the left arm. The first sound of Karotkoff was used for systolic pressure and the disappearance of sound as the diastolic pressure.

Arterial oxygen saturation was estimated with a Biox II ear oximeter. The subject's right ear lobe was vigorously rubbed with

rubbing alcohol and a gauze square until reddened. The alcohol was allowed to evaporate and the oximeter transducer was then attached to the earlobe. Arterial oxygen saturation was estimated while standing prior to exercise and during the last 30 seconds of each 2 minute stage. Delta oxygen saturation (DO_{2sat}) was calculated by subtracting the resting reading from the reading at maximal exercise.

Oxygen uptake (VO_2), carbon dioxide production (VCO_2), ventilation (V_e), breathing frequency (f_b), tidal volume (V_t), and expired flow were measured by a Beckman Metabolic Cart (MMC). All gas measurements were correlated to STPD conditions, except for V_e and V_t, by software in the MMC. V_e and V_t are expressed at BTPS conditions. The subject, with his nose occluded with a noseclip, breathed through a two-way valve (Collins #21098) which was attached to the volume measuring turbine inside the MMC via smooth bore tubing with an internal diameter of 38 mm. The MMC has been validated against breath-by-breath and conventional Douglas bag systems by Jones (1984), and found to be at least as accurate as the conventional Douglas bag system. Correlations between the MMC and the Douglas bag system reference system were 0.996 for V_e, 0.997 for steady state VO_2 and 0.994 for steady state VCO_2. The oxygen and carbon dioxide analyzers were calibrated with reference gases, measured with the Scholander (1947) apparatus, prior to each test. The volume measuring turbine on the MCC was calibrated at three flow rates prior to each test, with a 0.9 liter syringe. Calibration of the oxygen and carbon dioxide analyzers were checked following each test to

insure that calibration was maintained during each test. No tests had to be repeated due to analyzer drift during the course of testing. Predicted VO_{2max} was calculated according to the formula proposed by Bruce (1973).

Data Analysis

Differences between the two groups were compared with two-tailed t tests for independent samples using the t test procedure in the Statistical Analysis System, 1982. A p value of < 0.05 was considered to be significant. Correlations and regression functions were calculated with the General Linear Model procedure in the Statistical Analysis System (Statistical Analysis System Institute 1982).

CHAPTER IV

RESULTS

Characteristics of the Subjects

Eleven COPD patients (8 males and 3 females) and 8 healthy male subjects were tested. Characteristics, mean ± standard deviation, of the subjects are shown in Table 4. The only significant difference was that the healthy subjects were heavier.

TABLE 4. Characteristics of Subjects

	COPD	Healthy	p
Age	62.1 ± 10.1	57.0 ± 4.4	0.15
Mass (kg)	67.6 ± 13.4	86.2 ± 17.6	0.02
Height (cm)	172.2 ± 9.1	179.3 ± 6.4	0.07

Resting Pulmonary Function

Results of resting pulmonary function are shown in Table 5. As expected, the healthy subjects performed much better than the patients. Variable names following by the "%" sign represent the percentage of expected value for the variable.

Several derived measures of pulmonary function were calculated (Table 6). These calculations are not a part of the usual clinical evaluation and were included in an attempt to correct PFT for degree

TABLE 5. Resting Pulmonary Function

	COPD	Healthy	p
FVC (l)	2.81 ± 1.00	4.68 ± 0.59	0.0001
FVC%	77.4 ± 25.4	107.6 ± 8.6	0.002
$FEV_{1.0}$(l)	1.24 ± 0.41	3.88 ± 0.53	0.0001
$FEV_{1.0}$%	46.0 ± 19.7	115.6 ± 11.8	0.0001
FEF (l/sec)	0.47 ± 0.20	4.22 ± 1.13	0.0001
FEF%	14.6 ± 9.0	106.4 ± 26.8	0.0001
PEF (l/sec)	4.29 ± 1.38	9.74 ± 2.27	0.0001
PEF%	56.7 ± 18.0	109.9 ± 25.6	0.0001
MVV (l/min)	50.8 ± 16.9	117.6 ± 26.0	0.0001
MVV%	42.9 ± 17.1	116.9 ± 17.6	0.0001
TLC (liters)	5.94 ± 1.73	7.23 ± 0.86	0.08
TLC%	99.2 ± 24.1	107.5 ± 6.1	0.3
RV (liters)	2.82 ± 1.54	2.18 ± 0.39	0.20
RV%	155.2 ± 82.9	118.4 ± 4.7	0.18
D_{LCO} (ml/min/mm Hg)	15.1 ± 8.1	27.1 ± 4.7	0.0017
D_{LCO}%	71.7 ± 35.2	106.4 ± 15.0	0.01

TABLE 6. Derived Measures of Pulmonary Function

	COPD	Healthy	p
$FEV_{1.0}$/FVC	0.45 ± 0.11	0.82 ± 0.06	0.0001
$FEV_{1.0}$/KG(ml/kg)	18.6 ± 6.5	45.3 ± 3.1	0.0001
MVV/KG ($liters \cdot min^{-1} \cdot kg^{-1}$)	0.75 ± 0.21	2.03 ± 0.37	0.0001
RV/TLC	0.46 ± 0.13	0.30 ± 0.05	0.0023

of airway obstruction and body mass. As expected, the results indicate significant obstruction for the COPD patients.

Maximal Exercise Testing

The results of maximal exercise testing are shown in Table 7. There were no complications resulting from exercise testing. All tests were stopped because of shortness of breath in the case of the COPD patients, or generalized fatigue and/or shortness of breath in the healthy subjects.

TABLE 7. Maximal Exercise Data

	COPD	Healthy	p
$VO_2max(ml \cdot kg^{-1} \cdot min^{-1})$	14.0 ± 4.0	30.8 ± 5.6	0.0001
$VO_2max\%$*	53 ± 21	95 ± 19	0.0003
Heart rate (beats/min)	130.0 ± 9.3	163.5 ± 7.9	0.0001
HR, % of predicted	82.6 ± 7.8	100.4 ± 6.0	0.0001
V_e (liters/min-BTPS)	35.2 ± 9.3	87.9 ± 14.5	0.0001
V_t (liters-BTPS)	1.21 ± 0.24	2.85 ± 0.32	0.0001
RER	0.91 ± 0.07	1.08 ± 0.05	0.0001
Peak flow (liters/second)	2.67 ± 1.07	5.65 ± 1.12	0.0001
DO_{2sat}	-3.8 ± 3.4	-1.4 ± 3.4	0.14

*Estimate based on age and sex from Bruce, 1973.

Predicting Maximal Oxygen Consumption

One of the purposes of this study was to determine if maximal oxygen uptake could be predicted from resting measures of pulmonary function. This section presents regression equations predicting oxygen uptake expressed as $ml \cdot kg^{-1} \cdot min^{-1}$ and liters/min from resting measures of PFT.

Numerous regression equations using $ml \cdot kg^{-1} \cdot min^{-1}$ as the dependent variable were evaluated, however only two models were reasonably accurate and fulfilled the homoscedasticity assumption of regression analysis, MVV/KG and PEF, Table 8. The homoscedasticity assumption of regression requires that the variance of the data be approximately equal across the entire range of data (Downie and Heath 1974). Over two dozen multiple regression models were tested, but all were either nonsignificant or violated assumptions of regression analysis. Scatter plots of the data for each variable are shown in Figures 1 and 2.

TABLE 8. Regression Models Predicting $VO_{2max}(ml \cdot kg^{-1} \cdot min^{-1})$

MVV/kg	Y = 5.326 + 12.174 X MVV/KG	r = 0.90, S.E.E. = 4.4 ml/kg/min
PEF%	Y = 6.19 + 2.259 X PEF%	r = 0.79, S.E.E. = 6.4 ml/kg/min

Y = oxygen uptake $(ml \cdot kg^{-1} \cdot min^{-1})$

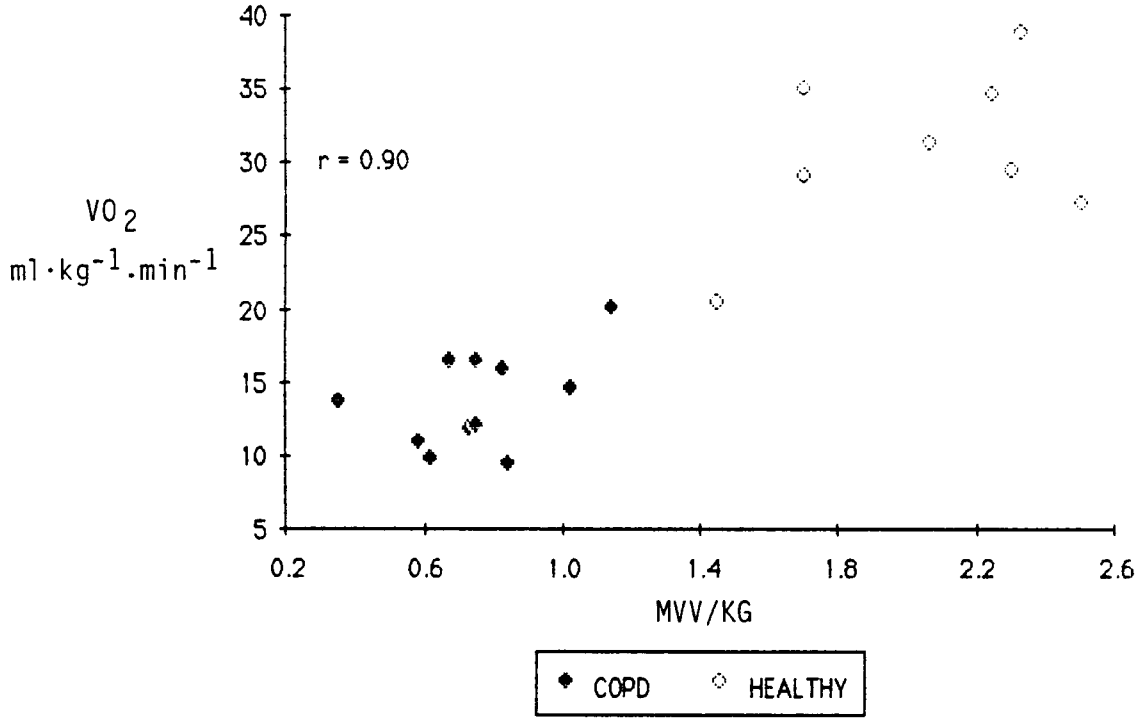


FIGURE 1. Scatter plot of VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) vs. MMV/KG.

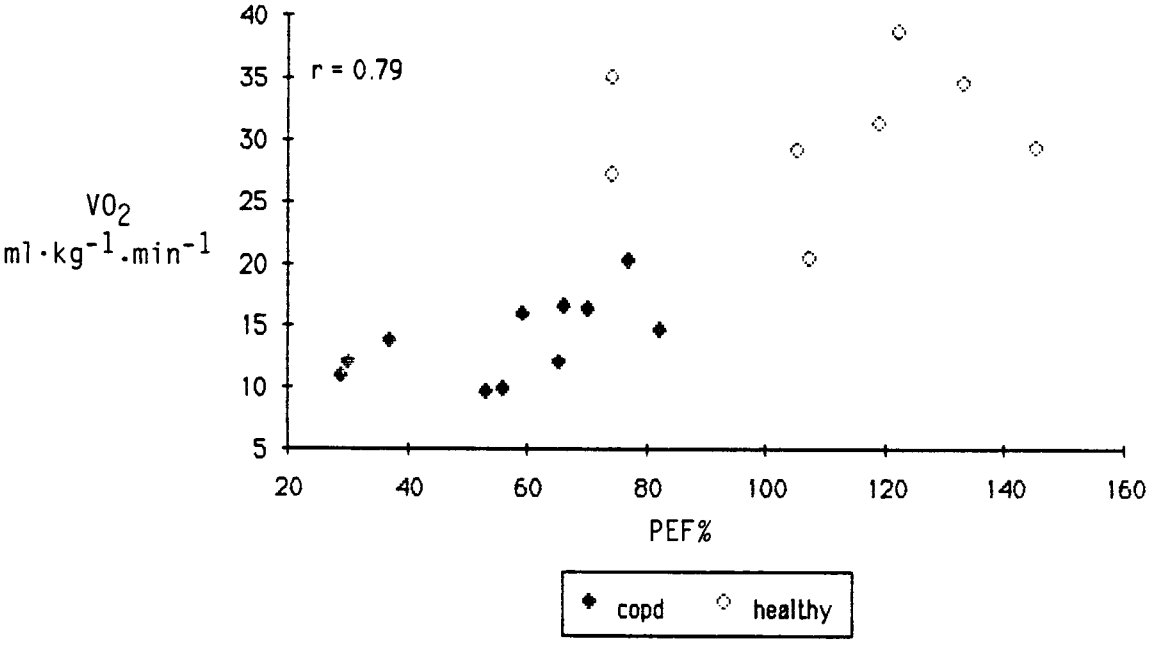


FIGURE 2. Scatter plot of VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) vs. PEF%.

Numerous regression models were calculated predicting VO_{2max} (l/min) from resting and derived measures of PFT. Two regression models predicting oxygen uptake in liters/minute met the assumptions of regression analysis, PEF and D_{LCO}, and were reasonably accurate, Table 9. One multiple regression equation, using PEF and D_{LCO}, was significant, r = 0.93.

TABLE 9. Regression Models Predicting VO_{2max} (liters/min) From Resting Measures of PFT

PEF	Y = 0.0326 + 0.2437 X PEF	r = 0.89, S.E.E. = 0.413 1/min
D_{LCO}	Y = 0.0041 + 0.8166 X D_{LCO}	r = 0.83, S.E.E. = 0.507 1/min
PEF & D_{LCO}	Y = -0.2282 + 0.167 X PEF + 0.038 X D_{LCO}	r = 0.93, S.E.E. = 0.34 1/min

Y = oxygen uptake (liters/minute)

Scatter plots showing the relationship between PEF and D_{LCO} and oxygen uptake (liters/min) are shown in Figures 3 and 4, respectively. Figure 5 shows the relationship between the predicted and measured oxygen uptake for the multiple regression equation using PEF and D_{LCO}.

In general, VO_{2max} expressed as $ml \cdot kg^{-1} \cdot min^{-1}$ tended to be more highly correlated with PFT measures expressed as a percentage of the

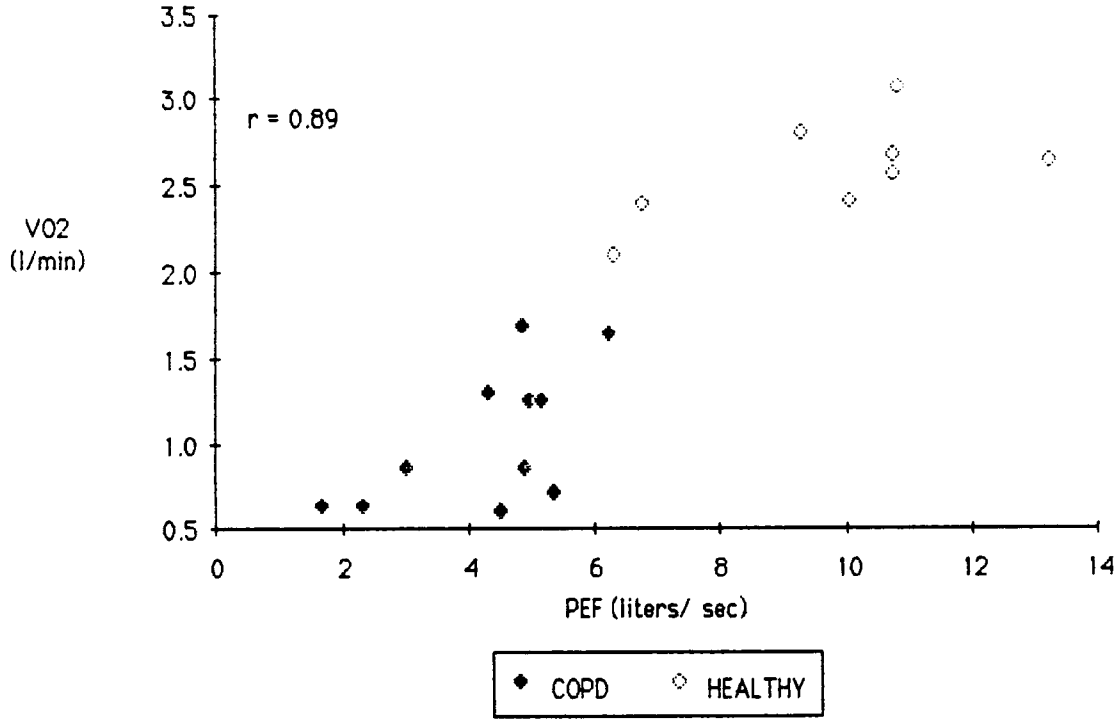


FIGURE 3. Scatter plot of PEF vs. VO_{2max} (l/min).

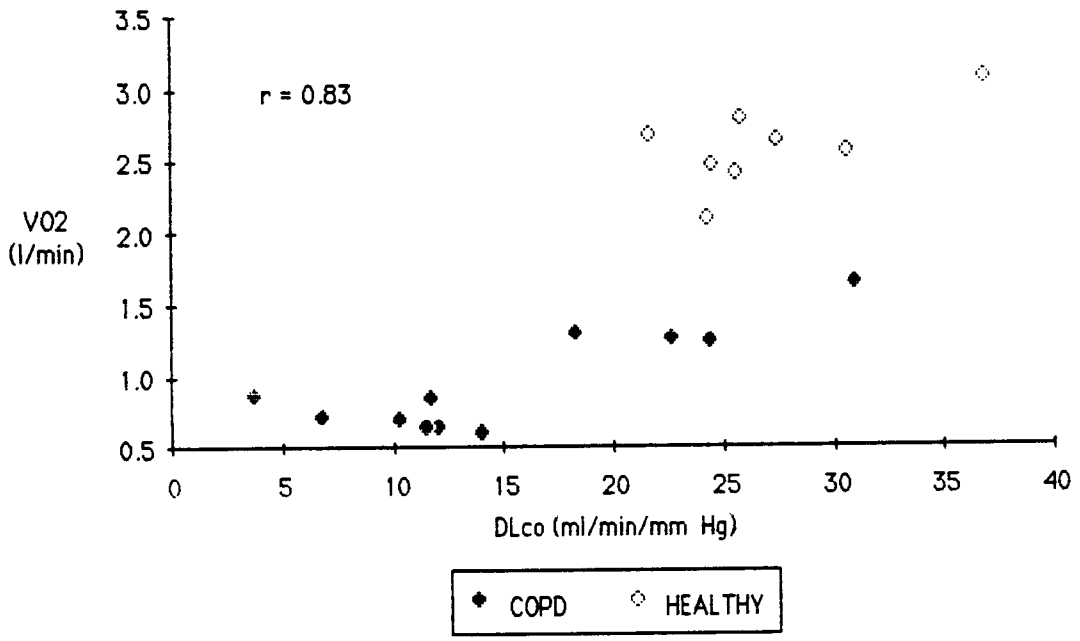


FIGURE 4. Scatter plot of D_{LCO} vs. VO_{2max} (l/min).

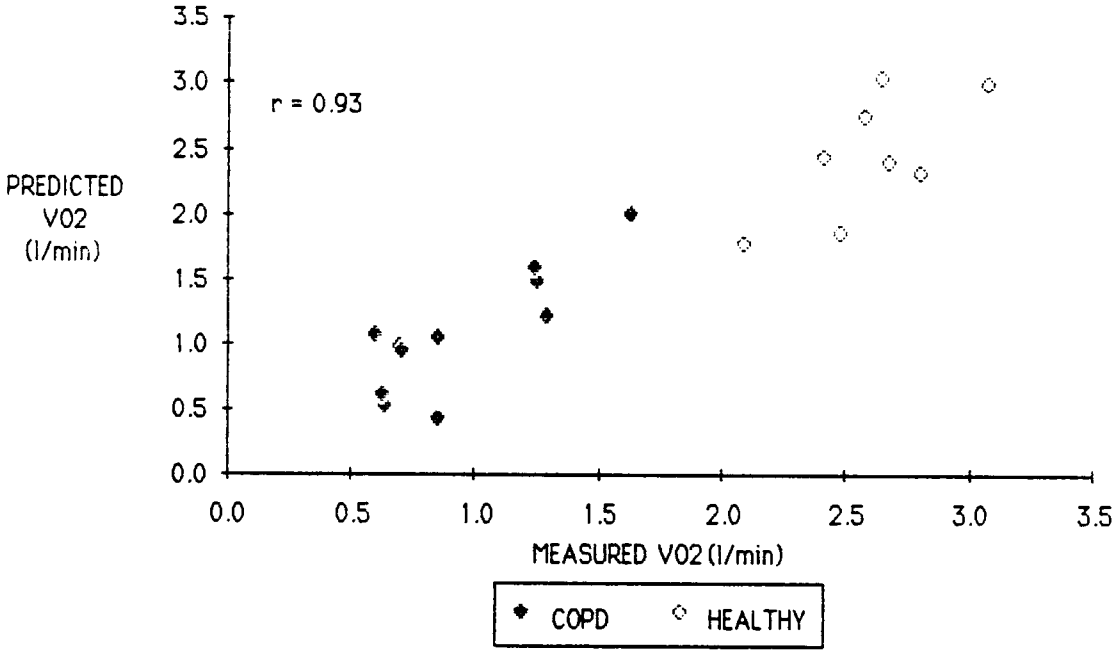


FIGURE 5. Predicted vs. measured oxygen uptake using multiple regression model.

expected value, while maximal oxygen uptakes expressed in liters/min were more highly correlated with the absolute value of the PFT measures.

The small number of healthy subjects and the relatively small range of values for PFT prevented a valid use of regression analysis within this group. Some of the correlation coefficients were very high, ($ml \cdot kg^{-1} \cdot min^{-1}$ and $FEV_{1.0}$, $r = -0.86$, $p < 0.001$), but this was largely due to the fact that most of the PFT data points were within 20% of each other (96-117% of expected), and any point outside of this range had an inflated effect on the correlation. Removing one subject's data that could be considered an "outlier" reduced the correlation coefficient to -0.23, which was not significant.

Two variables were moderately good predictors of maximal oxygen uptake ($ml \cdot kg^{-1} \cdot min^{-1}$) within the COPD group, PEF%, $r = 0.60$, $p < 0.05$, and D_{LCO}, $r = 0.67$, $p < 0.03$. The correlation between D_{LCO} and VO_{2max} was similar to that reported by Jones (1971) for DL_{CO} and maximal power output, $r = 0.60$. The correlation between PEF% and maximal oxygen uptake, expressed as liters per minute, was essentially the same as for $ml \cdot kg^{-1} \cdot min^{-1}$, $r = 0.58$, $p < 0.05$, while the correlation for D_{LCO} was much higher, $r = 0.81$, $p < 0.002$.

Ventilatory Patterns During Exercise

Figures of minute-by-minute ventilatory patterns (ventilation, tidal volume and frequency of breathing) for each subject are in Appendix B. For clarity, no more than four subjects are included on a single figure. COPD patients are labeled "C" and healthy subjects are labeled "H" in the legends for each figure. The ventilatory responses of the COPD patients were grossly abnormal. Ventilation increased little as the tests progressed, in contrast to the normal curvilinear response of the healthy subjects.

The ventilatory patterns used by the subjects at maximal oxygen uptake are given in Table 10. The ratio of tidal volume divided by FVC was significantly lower in the patients than in the healthy subjects, while the opposite was true for the ratio of maximal ventilation divided by MVV. The frequency of breathing and the ratio of peak $flow_{ex}$/peak $flow_{rest}$ did not differ between groups.

TABLE 10. Ventilatory Patterns at Maximal Exercise

	COPD	Healthy	p
V_t/FVC	0.47 ± 0.13	0.62 ± 0.11	0.01
V_e/MVV	0.74 ± 0.25	0.62 ± 0.22	0.03
F_b (breaths/minute)	31.7 ± 7.8	32.0 ± 4.1	0.9
Peak $flow_{ex}$/peak $flow_{rest}$	0.68 ± 0.30	0.62 ± 0.22	0.5

CHAPTER V

DISCUSSION

Resting Pulmonary Function

As expected, the COPD patients had significantly lower values for pulmonary function, whether expressed in absolute terms or a percentage of the expected value. The patients' low scores in $FEV_{1.0}$, FEF_{25-75} and PEF are consistent with the diagnosis of severe COPD. The only measures of resting PFT that were not different between groups were TLC and RV. The patients' RV% was above 100% of the expected value, but relatively low for patients with severe COPD. This may be a result of the method of measuring RV, nitrogen washout. This method is based on "washing" the entire lung of nitrogen. If areas of the lung have significant air trapping, that portion of the lung will not contribute to the measurement of lung volume, and the RV will be underestimated. Body plethysmography usually results in greater RV than nitrogen washout (West 1978), but the equipment was not available.

Derived Measures of Pulmonary Function

The $FEV_{1.0}$/FVC and $FEV_{1.0}$/KG ratios were significantly lower in the patient group, indicating that $FEV_{1.0}$ was low, whether expressed as a percentage of FVC or as ml per kg of body mass. The MVV/KG ratio was also lower in the patient group. This was expected, as the correlation between $FEV_{1.0}$ and MVV was 0.96 for the entire

subject pool. RV/TLC was higher in the patients, indicating lung hyperinflation, which is consistent with the diagnosis of COPD.

Maximal Exercise Data

The healthy subjects performed significantly better than the patients on nearly all measurements. Expressing VO_{2max} as a percentage of the expected value with equations proposed by Bruce (1973), the healthy subjects achieved 95% of the expected value, while the patients reached only 56% of the expected VO_{2max}. The COPD patients experienced about twice as much of a decrease in oxygen saturation as the healthy subjects, but this was not significant ($p > 0.14$).

The premise that the COPD patients were limited by the ventilatory response to exercise is supported by four factors:

1. The ventilatory response of the COPD patients was grossly abnormal. The response was "flat," i.e., it increased very little in response to increases in work, while the healthy subjects increased ventilation as the work rate was increased;

2. Also, the inability to hyperventilate during exercise is supported by the lower maximal RER (0.91 vs 1.08, $p < 0.0001$) of the COPD patients;

3. The ratio of Ve_{max}/MVV was higher in the COPD patients (74% vs 64%, $p < 0.03$) than the healthy subjects, indicating that the patients were utilizing a greater percentage of the respiratory system's ability to ventilate; and

4. The final factor indicating that COPD patients were limited by ventilation was that the patients experienced severe shortness of breath, resulting in test termination, at relatively low maximal heart rates. The healthy subjects' maximal heart rate averaged 100.4% of the age-adjusted maximum (range 92-108%), while the COPD group averaged 82.6%, range (71-93%, $p < 0.0001$).

Predicting Maximal Oxygen Consumption From Resting Pulmonary Function

Several measures of resting pulmonary function were moderately good predictors of maximal oxygen consumption for the combined groups. Correlations, for variables that met the homoscedasticity assumption of regression analysis, ranged from 0.77 to 0.90. Several PFT parameters had high correlations, but violated the assumptions of regression and are not reported. Maximal oxygen uptake ($ml \cdot kg^{-1} \cdot min^{-1}$) was correlated with PEF%, $r = 0.79$ and MVV/KG, $r = 0.90$. Maximal oxygen uptake (1/min) was correlated with PEF, $r = 0.89$ and D_{LCO}, $r = 0.83$.

The one multiple regression model that reached statistical significance had a very high correlation coefficient, 0.93. However, the standard error of the estimate equalled 340 ml, so the 95% confidence limits of the model has a range of 1.36 liters from the upper to lower limits. Despite the high correlation coefficient for this model, the variation included in the 95% confidence limits means that other factors probably contribute significantly to maximal oxygen

uptake. The significance of this model lies in the fact that maximal oxygen uptake increased dramatically as performance of these two measures (PEF and D_{LCO}) of resting PFT increased from severely compromised to normal levels.

Ventilatory Patterns at Maximal Exercise

The ratio of V_t/FVC was significantly lower in the patient group. Åstrand (1977) reported that healthy subjects utilize approximately 50-55% of FVC during exercise. The healthy subjects in the present study were slightly above the reported figure (62%), while the COPD patients were slightly below (47%), or about 25% less than the healthy subjects. The difference in the ratios was not a result of an unusually large FVC on the part of the COPD patients, since their FVC was lower than the healthy subjects. The ratio of maximal V_e/MVV was significantly greater in the patient group. Several authors have interpreted this finding as indication that ventilation limited exercise (Brown 1985a; Jones 1971; and Belman 1980).

The frequency of breathing at maximal oxygen uptake did not differ between groups. The relationship between age and maximal frequency of breathing is a poorly defined quantity. Entertainment of breathing with walking is a possibility in the present study, but other authors who have administered cycle ergometer tests to similarly aged subjects have reported similar maximal breathing frequencies, while younger subjects have greater maximal breathing frequencies. Folinsbee (1983) reported that young (mean age = 21)

untrained subjects achieved a maximal breathing frequency of 49, while highly trained cyclists reached 63 breaths per minute. Adams et al. (1972) administered maximal treadmill tests to 20 men with an average age of 64.8 $\pm$ 2.8 years and found the maximal respiratory rate to be 31.8 breaths per minute. Bradley reported the maximal respiratory rate of seven subjects while breathing room air and a oxygen/helium mixture. Maximal breathing frequencies for these patients were 22 for air and 24 for oxygen/helium. Brown (1985b) reported the maximal frequency of breathing of 11 COPD patients (mean age 61 $\pm$ 5) being tested to evaluate the reproducibility of maximal exercise testing on three occasions. The mean breathing frequencies were 34, 33 and 33 breaths per minute. It appears that the ventilatory frequency achieved by the COPD patients in the present study is similar to other studies, using subjects of the same age, with or without COPD. The decreasing maximal breathing frequency with age may be a normal part of aging, similar to the well documented age-related decrease in maximal heart rate.

Another possible reason for this lower frequency of breathing may be lowered sensitivity of the respiratory centers to CO_2. Brischetto et al. (1984) reported that the slope of ventilatory response to hypercapnia was lower in older subjects (Δ VE/ΔVCO_2 = 1.64 $\pm$ 0.21 vs. 2.44 $\pm$ 0.40 l/min/mm Hg) than in younger subjects. An alternate explanation might be that the older subjects are less likely to push themselves to the same level of exertion as the younger subjects.

The ratios of peak expiratory flow at rest/peak expiratory flow during exercise were not different between groups, indicating that the absolute magnitude of resting peak flow might be a good predictor of maximal oxygen consumption. The correlation between VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) and PEF% was 0.79, $p < 0.0001$. The correlation between VO_{2max} (liters/min) and PEF was 0.89, $p < 0.0001$.

Conclusions

1. Maximal oxygen uptake (1/min) can be reasonably predicted from resting PFT using the equation:

$$Y = -0.2282 + 0.167 \times PEF + 0.038 \times D_{LCO},$$

$r = 0.93$, S.E.E. = 0.34 1/min

2. The patients' lower maximal V_e was the result of smaller tidal volumes and smaller V_t/FVC ratios, rather than lower maximal frequencies of breathing or a lower peak exercise flow/peak resting flow ratio.

3. The COPD patients' exercise performance was probably limited by ventilatory reserve rather than cardiovascular reserve for the following reasons:

a. The ventilatory response to increasing work was "flat," it did not increase, or increased very slowly with increases in treadmill speed and grade.

b. The COPD patients' RER was substantially lower than the healthy subjects', indicating a relative lack of hyperventilation during maximal exercise.

c. The ratio of Ve_{max}/MVV was greater in the COPD patients, indicating the ventilatory reserves of the respiratory system were more heavily taxed.

d. The COPD patients stopped exercising at 83% of the age-predicted maximal heart rate due to dyspnea, while the healthy subjects achieved 100%.

Recommendations

It is apparent from the present study that maximal exercise performance is related to resting pulmonary function when comparing COPD patients and healthy subjects. The subjects in the present study represented the two extremes of pulmonary function: severe exercise impairment due to COPD and life-long nonsmokers. It might be informative to include subjects that smoke cigarettes, but do not have a diagnosis of COPD to determine if the predictive relationship found in these subjects persist.

The present study did not include any measures of inspiratory flow, at rest or during exercise. As discussed earlier, COPD often places the inspiratory muscles at a mechanical and physiological disadvantage for generating inspiratory pressure. Inspiratory mechanics and flow may be areas of important differences between COPD patients and healthy subjects.

The training studies using COPD patients have generally been poorly controlled. Training COPD patients with adequate control over the intensity, duration and frequency of exercise would probably help clarify whether these patients will benefit from exercise training.

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APPENDIX

APPENDIX A

INFORMED CONSENT FORM

DESCRIPTION OF THE PROJECT:

The purpose of this study is to compare the pulmonary function tests and maximal exercise tolerance of individuals with Chronic Obstructive Pulmonary Disease and age-matched healthy subjects. I understand that I will be given tests to determine how well my lungs function. The lung function tests will require me to breath as forcefully as possible into a mouthpiece while my nose is occluded.

Approximately one week after the lung function tests, I will take a maximal exercise test on a treadmill. The maximal exercise test will be monitored by a physician, and will continue until I am unable to continue exercising, or symptoms appear indicating the test should be stopped. During the exercise test, standard 12 lead electrocardiograms will be monitored to evaluate the functioning of my heart. Blood pressures will be obtained with a cuff placed around my left arm every two minutes. The amount of oxygen my body uses during exercise will be measured. This measurement will be accomplished by my breathing into a mouthpiece connected to measurement instrumentation. My nose will be occluded by a nose clip during the test. In addition, an ear oximeter clip will be attached to my ear lobe to monitor the amount of oxygen in my blood, but no blood samples will be taken. I understand the test will continue until I am no longer able to maintain the exercise pace. I can indicate that I am ready to stop the treadmill test at any time and my request will immediately be honored. I also understand that I will be required to remain in the testing area for at least 30 minutes following testing to insure that no complications of testing are present.

POTENTIAL RISKS AND DISCOMFORTS:

The rate of work required in the treadmill test is sufficient to produce fatigue. The risks involved with exercise include the possibility of a heart attack or death, but the risk is very small as was indicated by Gibbon and co-workers (Medicine and Science in Sports, 9:74, 1977). These workers reported an estimated death rate of 2.6 cases per 10,000 maximal stress tests. This figure includes subjects ranging in age from 10-84 and includes subjects with known heart disease. For comparison, in 1977 there were 1.32 deaths per 100 million miles traveled on the interstate highway system in the U.S. Standard emergency equipment and trained personnel will be immediately available, if needed. Exercise of this intensity may produce soreness

and slight muscular discomfort in the legs for 24-48 hours after the test.

I understand that this is a research project and is not required by my physician as a part of my therapy. I understand that this study may provide information that may help individuals with COPD at some date in the future. I also understand that I can have the results of my lung function and exercise testing explained to me, and a copy of all testing can be forwarded to my personal physician, if requested. Suggestions regarding appropriate levels and types of exercises can be given, based on the results of exercise testing.

In the event complication arise from the testing, the investigators are responsible for providing emergency medical attention for 30 minutes following pulmonary function testing and treadmill testing. I realize that I will be solely responsible for securing and paying for further medical attention and/or hospitalization. Fort Sanders Regional Medical Center and The University of Tennessee will not be liable for any injury or death resulting from this study.

My privacy will be protected during data analysis by the assignment of identification numbers, and at no time will I be identified by name in any presentations or publications arising from this study. No photographs of the testing will be made.

I have read the statement above and understand my role in the experiments and the risks involved. I have had the procedures explained to my satisfaction, and realize that the testing in question is for research purposes, and not a part of my routine medical care. I also realize that I will not be paid for my participation in this project. Any expenses incurred from my participation in this study will be my obligation, and I agree not to hold the University of Tennessee or Fort Sanders Regional Medical Center responsible in the event of injury or death resulting from participation in this study. The responsibility of the investigators and testing personnel is limited to providing emergency medical care immediately after testing, as stated above.

Any questions I have had have been answered to my satisfaction. I understand the nature of all procedures I have agreed to participate in. In addition, I am aware that:

1. I am entitled to have any further questions answered regarding the procedures;
2. I may withdraw my consent and discontinue participation at any time without penalty or prejudice toward me;
3. I will be given a copy of this agreement after I agree to participate and have signed the agreement.

Signature:_____ Date_____

Witness:_____ Date_____

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APPENDIX B

FIGURES FOR MINUTE-BY-MINUTE VENTILATORY PATTERNS

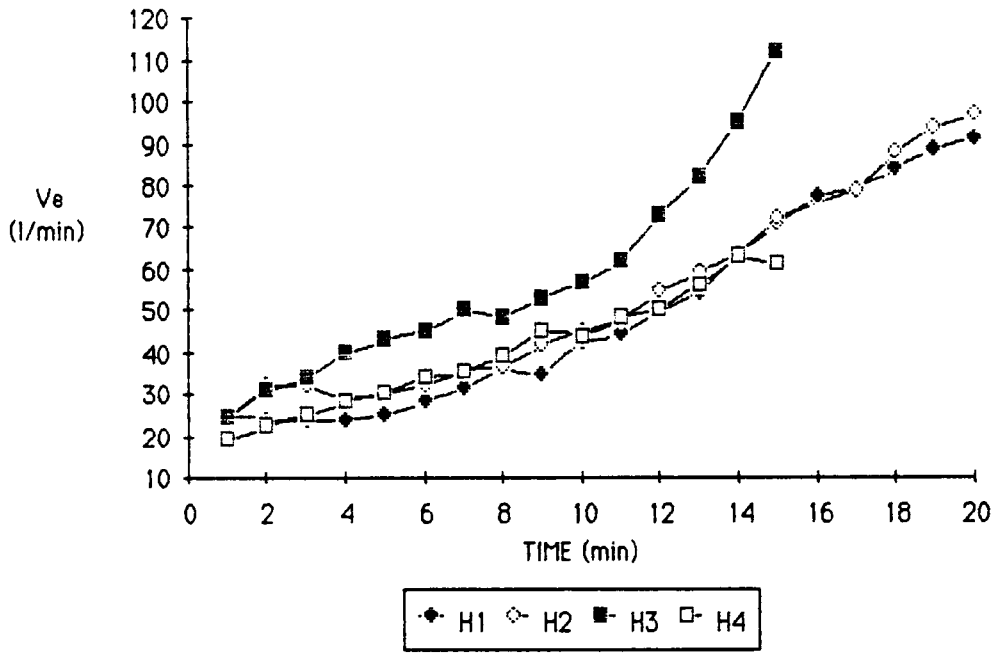


FIGURE 6. Minute-by-minute ventilation during treadmill test, healthy subjects 1-4.

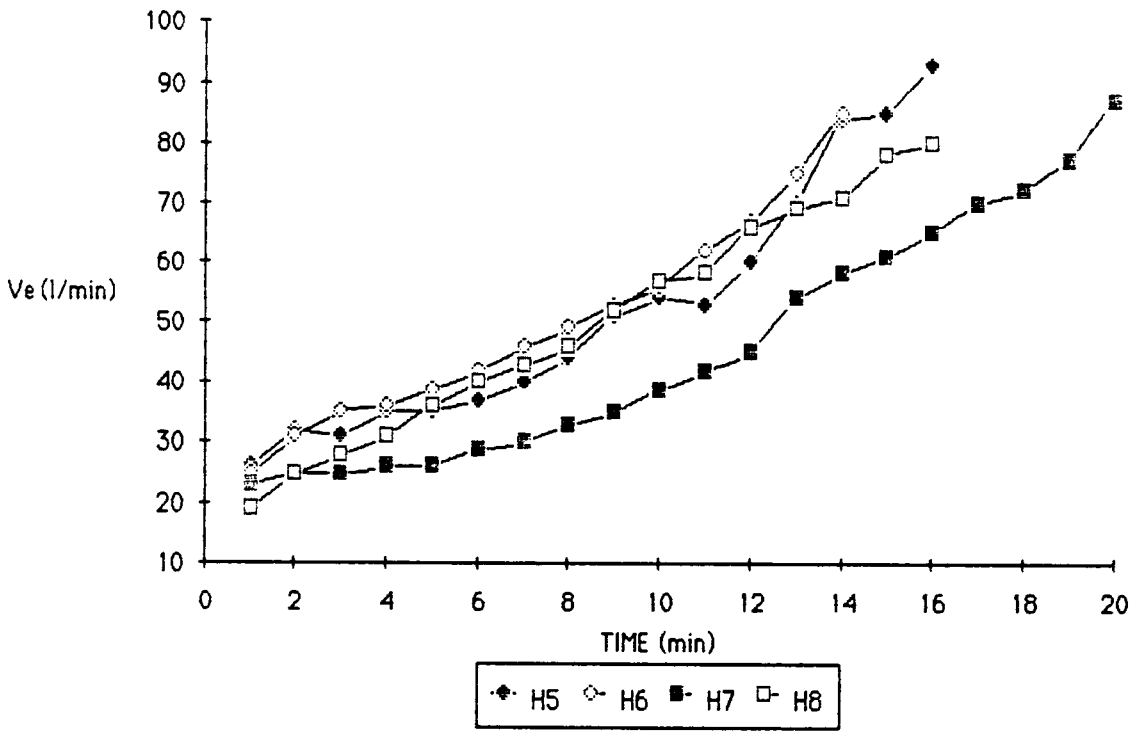


FIGURE 7. Minute-by-minute ventilation during treadmill test, healthy subjects 5-8.

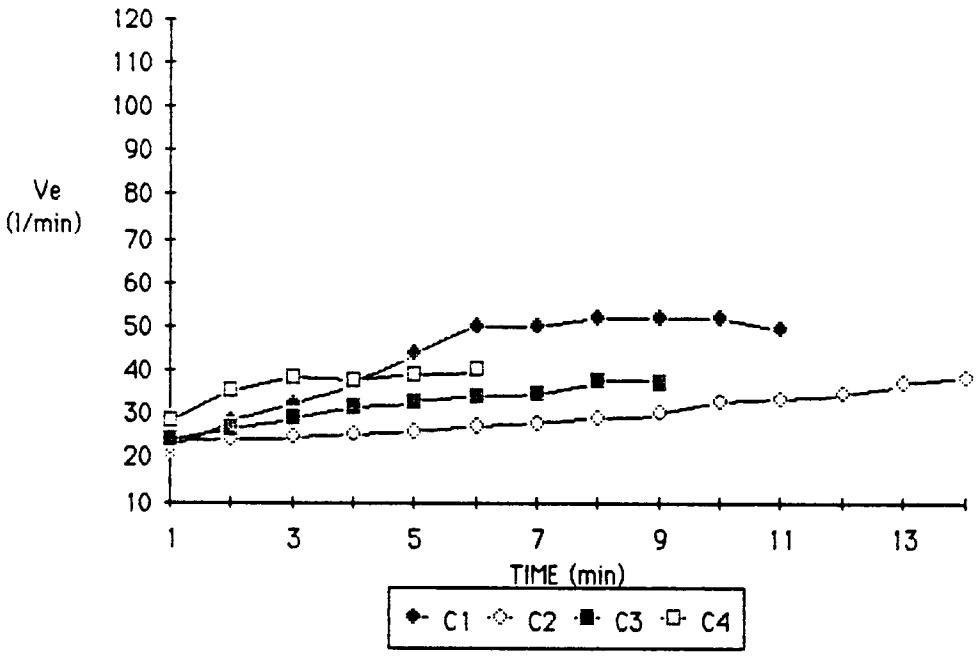


FIGURE 8. Minute-by-minute ventilation during treadmill test, COPD patients 1-4.

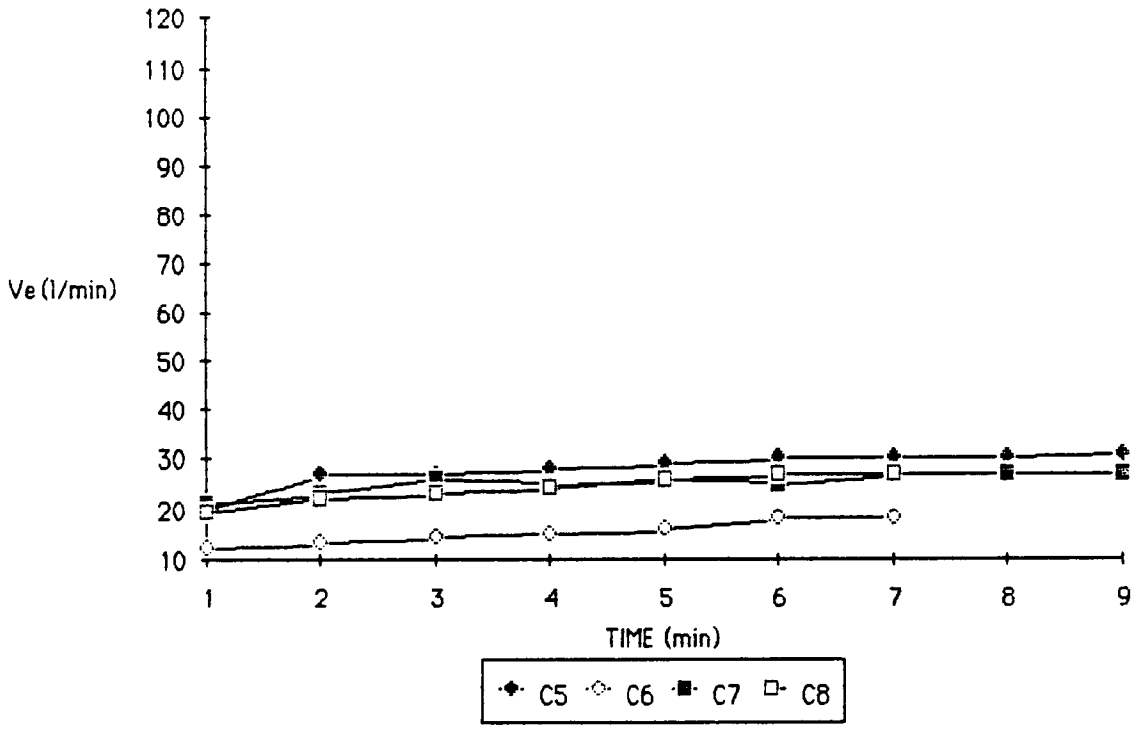


FIGURE 9. Minute-by-minute ventilation during threadmill test, COPD patients 5-8.

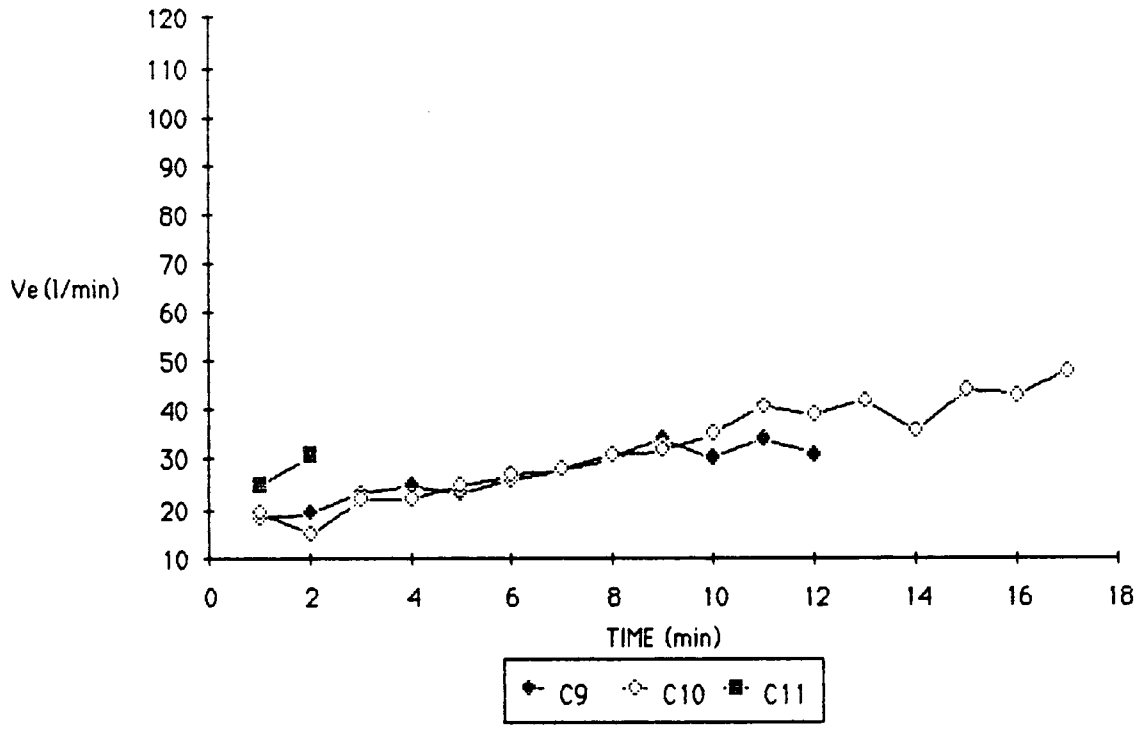


FIGURE 10. Minute-by-minute ventilation during treadmill test, COPD patients 9-11.

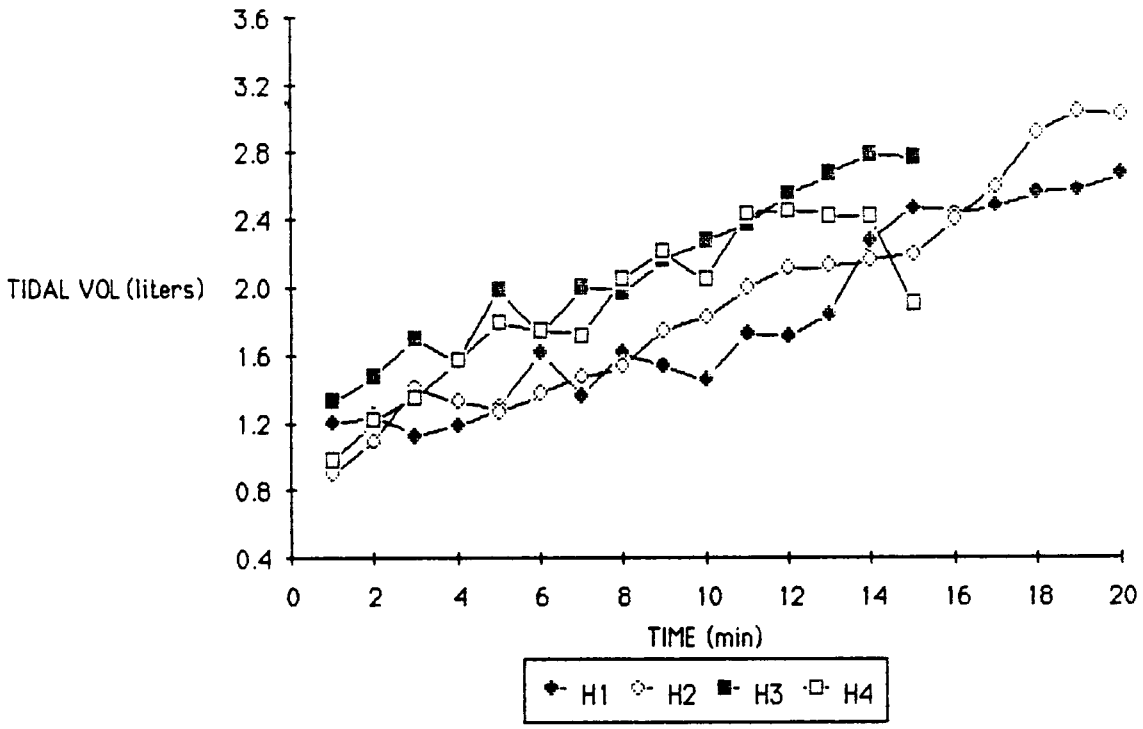


FIGURE 11. Minute-by-minute title volume during treadmill test, healthy subjects 1-4.

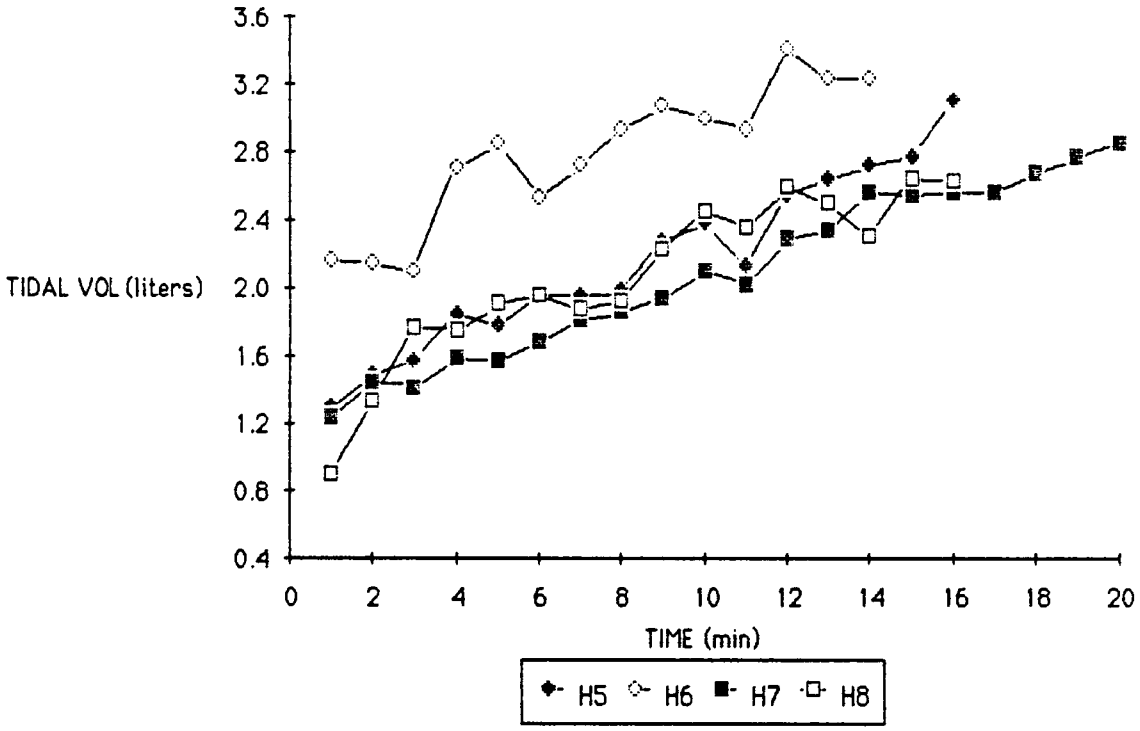


FIGURE 12. Minute-by-minute title volume during treadmill test, healthy subjects 5-8.

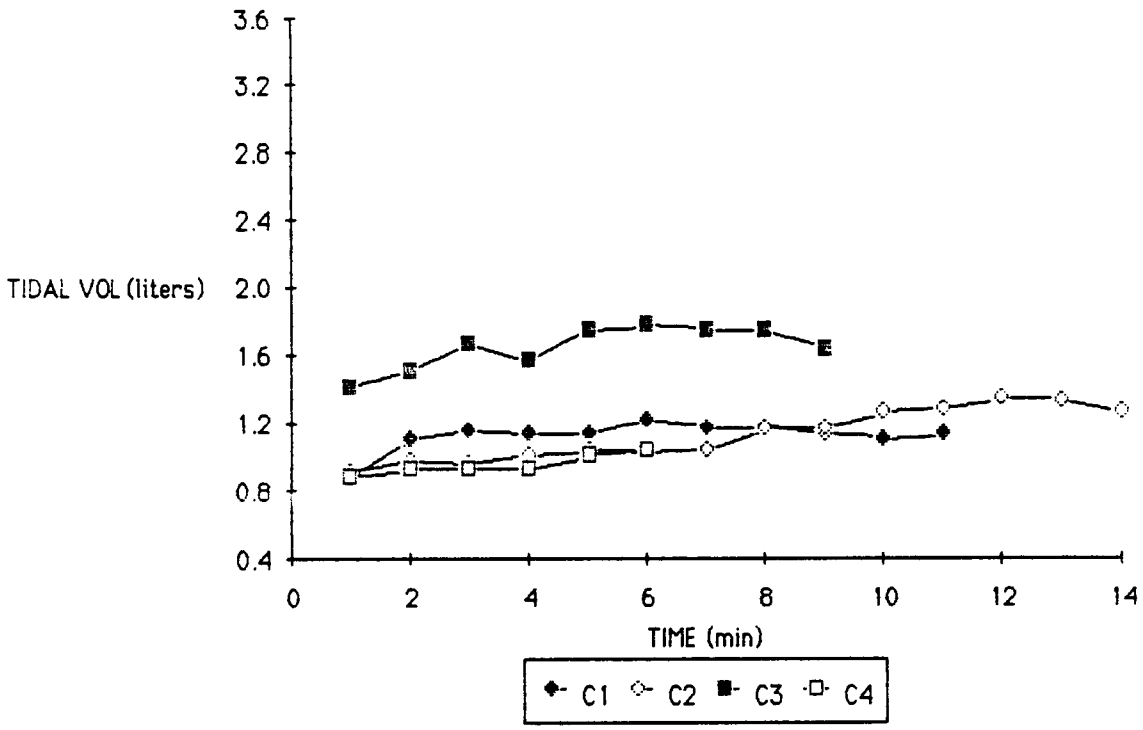


FIGURE 13. Minute-by-minute title volume during treadmill test, COPD patients 1-4.

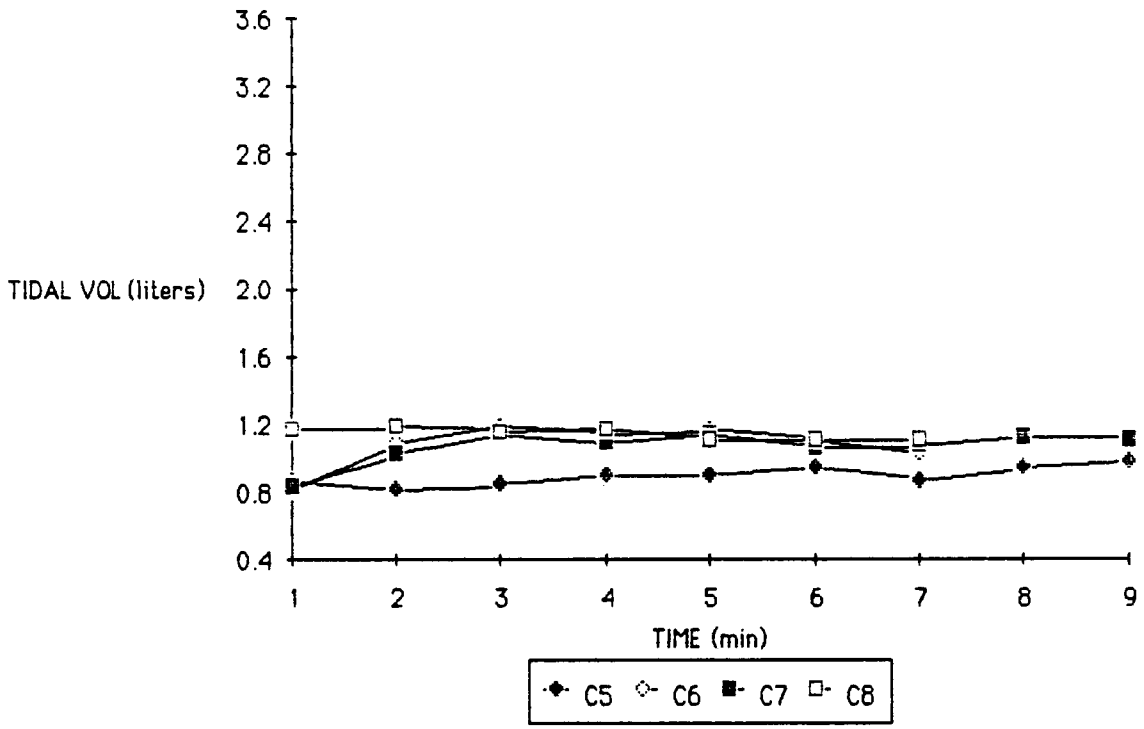


FIGURE 14. Minute-by-minute title volume during treadmill test, COPD patients 5-8.

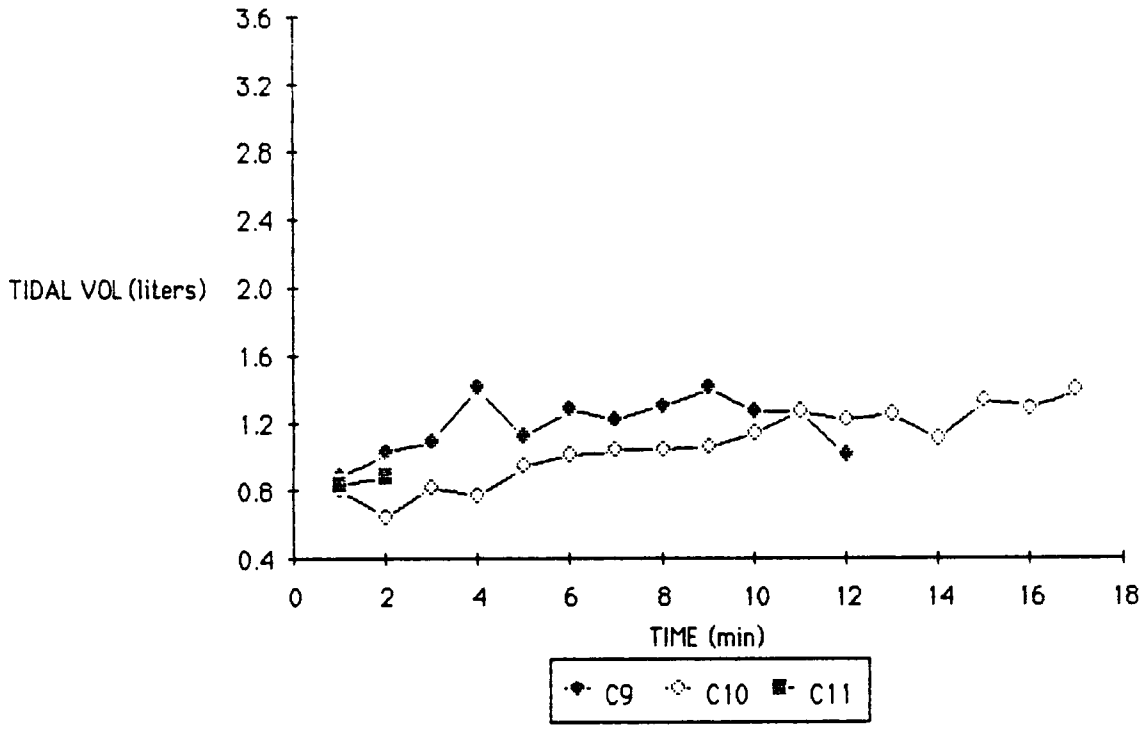


FIGURE 15. Minute-by-minute title volume during treadmill test, COPD patients 9-11.

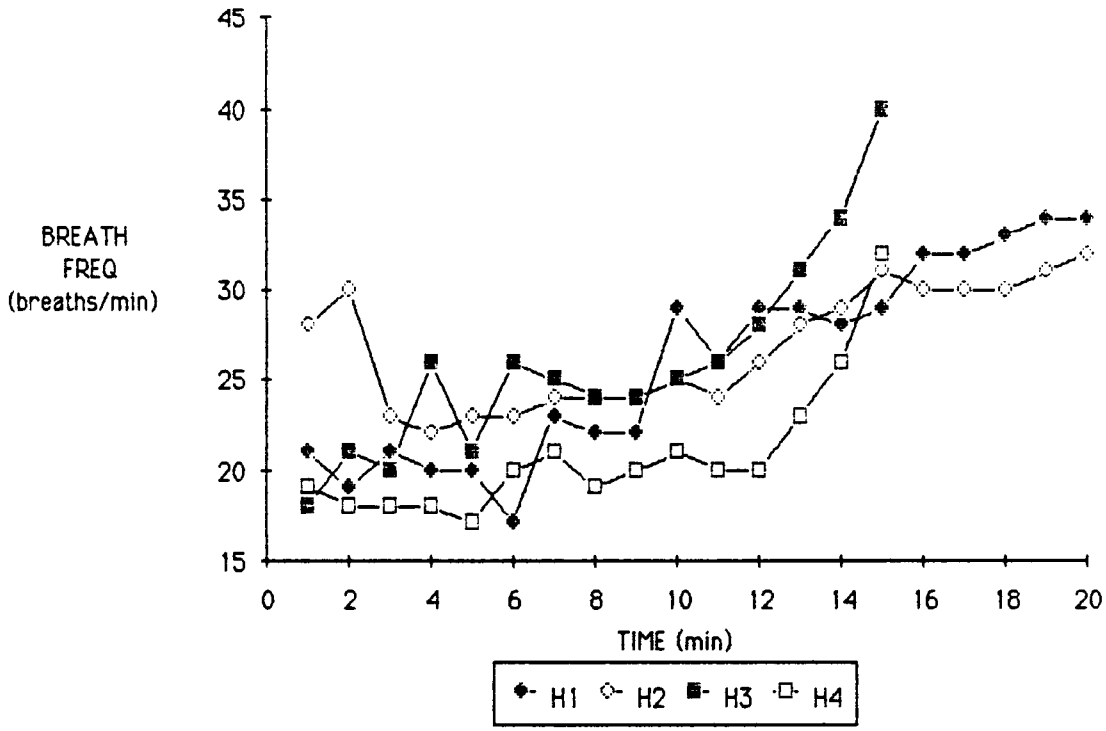


FIGURE 16. Minute-by-minute frequency of breathing during treadmill test, healthy subjects 1-4.

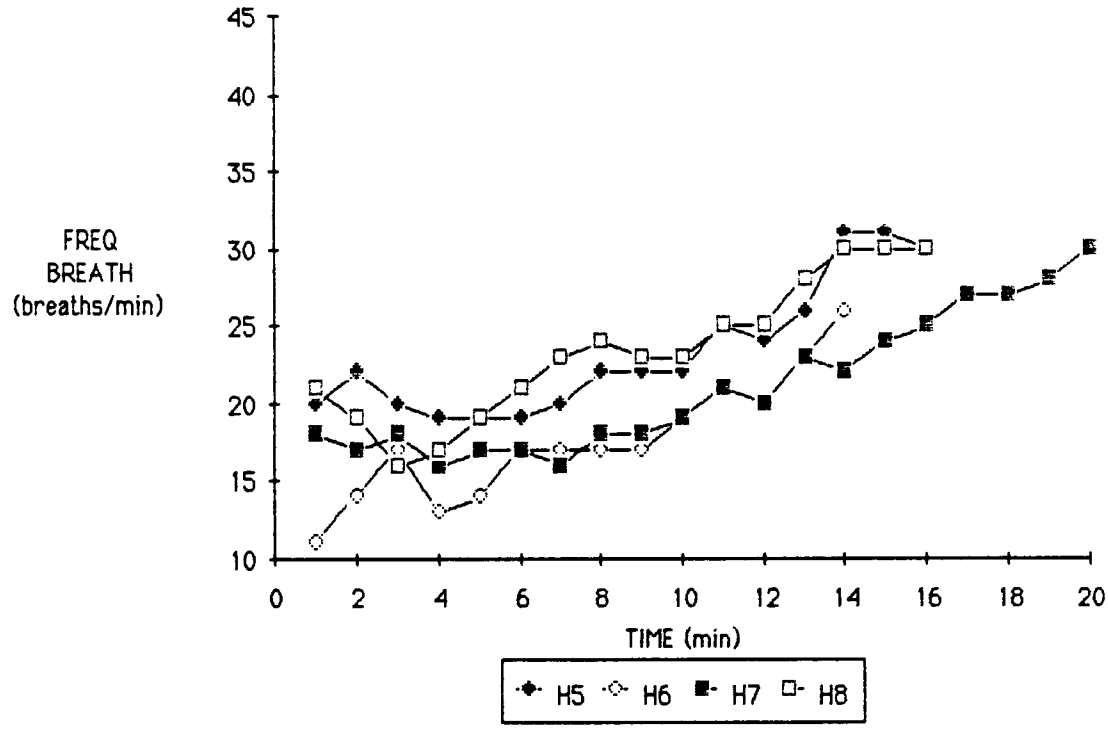


FIGURE 17. Minute-by-minute frequency of breathing during treadmill test, healthy subjects 5-8.

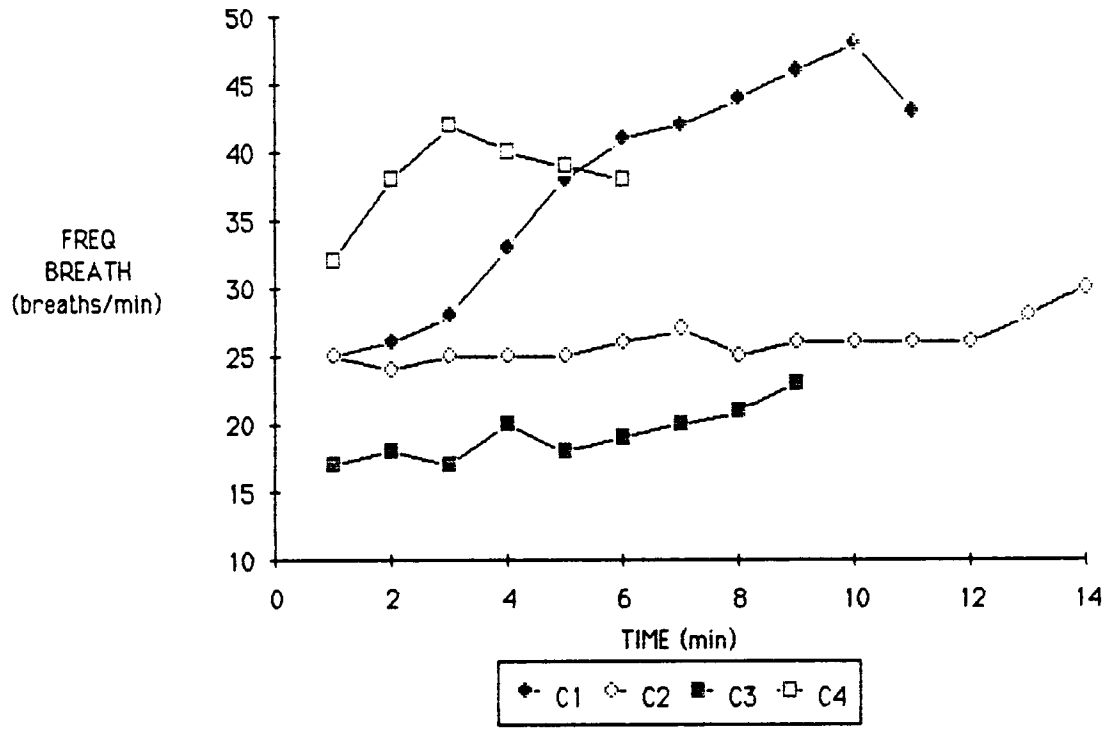


FIGURE 18. Minute-by-minute frequency of breathing during treadmill test, COPD patients 1-4.

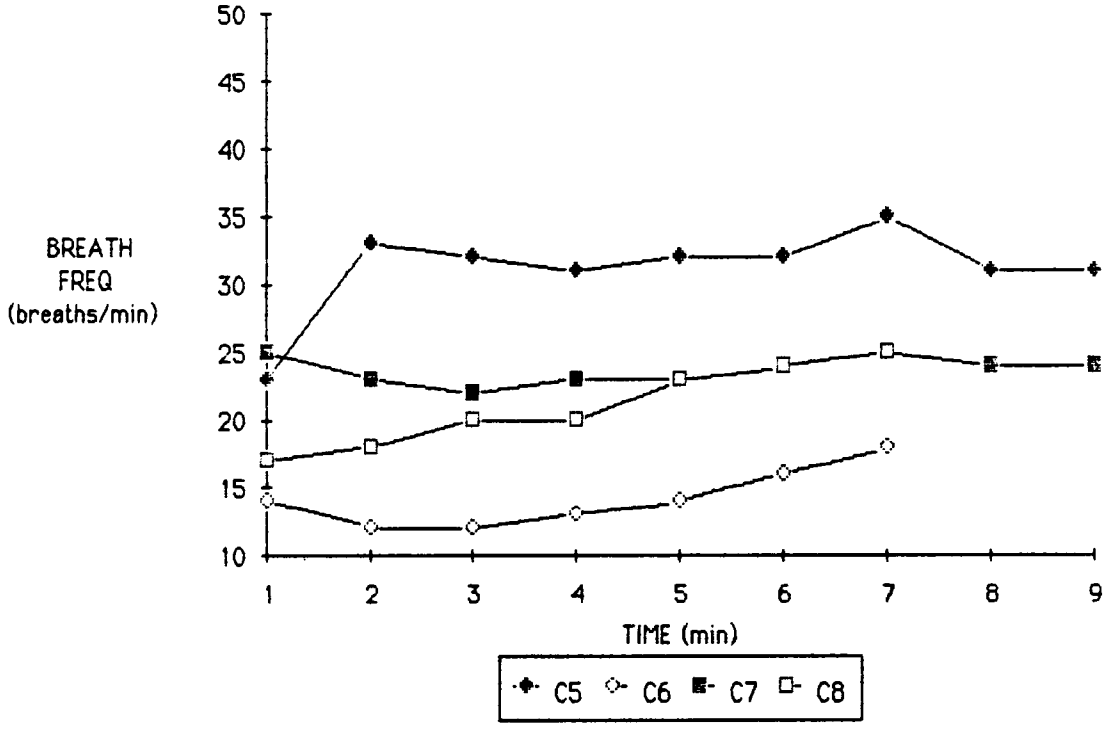


FIGURE 19. Minute-by-minute frequency of breathing during treadmill test, COPD patients 5-8.

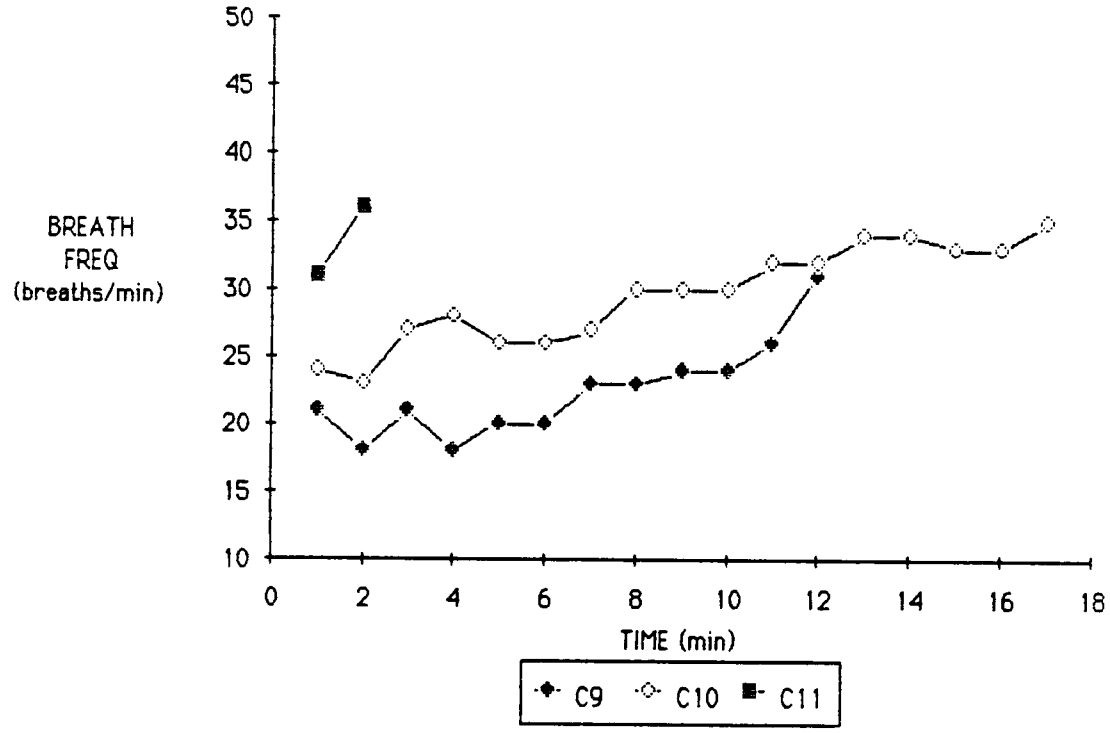


FIGURE 20. Minute-by-minute frequency of breathing during treadmill test, COPD patients 9-11.

VITA

Daniel Martin was born December 21, 1953 in Raceland Louisiana. He attended public schools in Houma, Louisiana and graduated from Terrebonne High School in June of 1971. The following September he entered The University of Tennessee, Knoxville on a track and field scholarship, graduating in March of 1976 with a Bachelor of Science in Physical Education. In September of 1977 he entered the University of Tennessee Center for the Health Sciences and graduated with a Bachelor of Science in Physical Therapy in December of 1978.

Daniel entered the doctoral program in Education in the fall of 1980 and graduated in August of 1985. Following graduation, he accepted a position in the Department of Physical Therapy at the University of Florida