

Cardiopulmonary Exercise Testing in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Introduction: Accurate assessment of the exercise capacity of patients with chronic obstructive pulmonary disease (COPD) is important for the dual purpose of exercise prescription and determining response to therapy. Currently, the clinical utility of cardiopulmonary exercise testing (CPET) of patients with COPD as part of their evaluation for pulmonary rehabilitation is not established. The aims of this study were to evaluate the role of CPET in determining maximal exercise capacity and the causes of exercise limitation in patients with COPD. **Materials and Methods:** The results of resting pulmonary function tests and CPET performed on 33 subjects with stable COPD as part of their evaluation for pulmonary rehabilitation were reviewed. Thirty-two of these patients had moderate or severe COPD. **Results:** Twenty-nine of the 33 patients were able to perform maximal exercise tests during CPET. Of these 29 maximal tests, the causes of exercise limitation were ventilatory limitation in 17 patients, significant oxygen desaturation in 1 patient and both ventilatory limitation and oxygen desaturation in 11 patients. Limb muscle dysfunction is a possible limiting factor in the 4 patients with sub-maximal tests. Physical deconditioning may be a contributory factor of exercise intolerance in 2 patients. Although there was significant correlation ($r = 0.597$, $P = 0.01$) between peak VO_2 percent predicted and FEV_1 percent predicted, there was marked variability of peak VO_2 for a given degree of airflow obstruction. **Conclusions:** CPET is useful for determining the causes of exercise limitation and for assessing the maximal exercise capacity of patients with COPD.

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Key words: Exercise capacity, Exercise limitation, Oxygen consumption, Pulmonary function, Pulmonary rehabilitation

Introduction

Exercise intolerance is a hallmark of chronic obstructive pulmonary disease (COPD). Although exertional symptoms may be mild at the outset, exercise limitation is the most disabling and distressing consequence of COPD for the majority of patients. It is somewhat surprising, therefore, that exercise testing is not commonly used in the evaluation of patients with COPD, in whom objective assessment of severity and response to therapy is mainly limited to pulmonary function tests performed at rest.

Cardiopulmonary exercise testing (CPET) is an integrative evaluation with gas exchange and ventilatory measurements added to the monitoring of the electrocardiogram and blood pressure during exercise. Recent technological improvements have enabled CPET, which was previously confined to the exercise physiologist's laboratory, to be conveniently and safely performed on patients in clinical settings. CPET is currently performed in some pulmonary rehabilitation programmes to determine

exercise-limiting factors for better candidate selection in addition to assessing functional capacity as accurate assessment of exercise capacity in COPD patients is important for the dual purpose of prescription of exercise training and determining response to therapy. However, while CPET has been advocated for routine use in the initial evaluation for rehabilitation of patients with COPD by some investigators,¹ its complexity and cost have been considered limiting by others.² Two different issues are of relevance to the clinical utility of performing CPET in COPD patients. Firstly, CPET is useful for determining the mechanisms limiting exercise only if patients with COPD are able to perform maximal tests during CPET. Many of these patients, however, are characterised by poor exercise tolerance and the possibility of maximal exercise testing in these individuals is largely uncertain. Secondly, CPET in COPD is necessary only if pulmonary function tests performed at rest cannot accurately predict the maximal exercise capacity in these patients. If exercise intolerance

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in COPD patients is determined mainly by limited ventilatory reserve during exertion, pulmonary function tests at rest should be closely correlated to the exercise capacity of these patients and exercise testing may therefore not be necessary.

The aims of this study were to evaluate the role of CPET in determining maximal exercise capacity and the causes of exercise limitation in patients with COPD.

Materials and Methods

The subjects in this study were patients with stable COPD as defined by the American Thoracic Society³ (ATS) who underwent CPET as part of their evaluation for pulmonary rehabilitation from July 1998 till November 1999. Patients who were previously determined to require supplemental oxygen at rest or during exercise were not included.

Each patient underwent evaluation of resting pulmonary function, including forced expiratory volume in one second (FEV₁), maximal voluntary ventilation (MVV), total lung capacity (TLC), and residual volume (RV) on the same day that CPET was conducted. The pulmonary function tests consisted of standard spirometry and lung volumes via whole-body plethysmography using the Jaeger Masterlab system (Jaeger, Wurzburg, Germany). The lung function tests were performed using standard protocols, and the ATS guidelines were used to determine acceptability.⁴ The MVV was directly measured in all patients using spirometry as previously described.⁵ At least 2 MVV manoeuvres were recorded with the 2 values within 10% of the mean of the measurements.

Symptom-limited CPET was performed using an electromagnetically braked cycle ergometer (Jaeger ER 900) after informed consent was obtained from all patients prior to exercise testing. CPET was performed under the supervision of a physician with defined criteria for stopping, such as serious cardiac arrhythmias, hypotension and electrocardiographic changes and severe oxygen desaturation. An incremental exercise protocol was used in which the work rate was increased by 5 watts per minute after an initial 3 minutes of unloaded pedalling. Standard 12-lead electrocardiograms were obtained at rest, every 3 minutes during exercise and for 5 minutes into the recovery phase while blood pressures were measured using a standard cuff sphygmomanometer at similar intervals. Measurements of mixed expired oxygen, mixed expired carbon dioxide and expired volume were determined at rest and every 10 seconds throughout exercise using a metabolic cart (JAEGER® Oxycon Alpha; ERICH JAEGER GmbH, Germany). Oxygen saturation (SaO₂) via pulse oximetry and heart rate by electrocardiography were recorded continuously throughout exercise and during recovery. At

the end of exercise, the reason/s for termination as well as the Borg dyspnoea score were obtained from the subjects.

The peak oxygen uptake (VO₂) was the highest observed during exercise. Anaerobic threshold (AT) was defined as

- 1) the point at which the ventilatory equivalent for O₂ (VE/VO₂) was minimal followed by a progressive increase,
- 2) the point after which the respiratory gas exchange ratio consistently exceeded 1, and
- 3) the VO₂ after which expired carbon dioxide increased non-linearly relative to oxygen consumption (V-slope).

The anaerobic threshold per cent (AT%) was defined as (VO₂ at AT/the predicted maximal VO₂) x 100. Predicted values for FEV₁, maximal VO₂ and maximal work rate were determined using the prediction equations from Chia et al,⁶ Wasserman et al⁷ and Jones et al,⁸ respectively.

The criteria for a maximal test in this study were:

- 1) peak VO₂ equal to or greater than 85% of the predicted value,
- 2) exercise terminated because of a serious electrocardiogram (ECG) abnormality,
- 3) maximal heart rate attained was greater than 85% predicted,
- 4) percentage of minute ventilation at peak exercise (VEmax) greater than 85% of MVV (ventilatory limitation), and
- 5) significant decrease in oxygen saturation of greater than 4%.

Exercise tests were considered maximal if subjects achieved one or more of these criteria.

For statistical analysis, the relationship between two sets of data was analysed using Pearson correlation test. Comparisons between groups were done with Student's *t* tests for normally distributed continuous variables and Mann-Whitney *U* tests for non-normally distributed continuous variables. A *P* value of less than 0.05 was considered to be statistically significant.

Results

The anthropometric and pulmonary function data of the 33 patients in this study are shown in Table I. The subjects included patients with mild to severe obstructive abnormalities with a wide range of FEV₁ predicted values, but the vast majority (97%) of them had moderate or severe COPD as defined by ATS.³

The dominant symptoms at peak exercise were dyspnoea in 20 patients (61%), leg fatigue in 8 patients (24%) and both dyspnoea and leg fatigue of equal intensity in 5 patients (15%). The Borg dyspnoea score of greatest frequency at peak exercise was 6.

Based on the criteria listed above, all except 4 patients were able to achieve maximal exercise tests. Of these 29

TABLE I: ANTHROPOMETRIC AND PULMONARY FUNCTION DATA[†]

	Mean $\pm$ SD	Range
Sex (M/F)	25/8	
Age (y)	69.2 $\pm$ 7.9	52 – 88
Body mass index	21.3 $\pm$ 3.6	13.3 – 30.0
FEV ₁ (L)	0.86 $\pm$ 0.26	0.48 – 1.8
FEV ₁ (% predicted)	45.7 $\pm$ 12.9	20.6 – 72.0
RV/TLC (%)	66.4 $\pm$ 8.9	39.5 – 85.8
CPET		
Peak VO ₂ (mL/min)	750 $\pm$ 195	381 – 1110
Peak VO ₂ (% predicted)	53.5 $\pm$ 17.4	21.6 – 92.0
Peak WR (W)	28.2 $\pm$ 14.2	0 – 55
Peak WR (% predicted)	28.6 $\pm$ 13.5	0 – 55.2
Breathing reserve (L)	2.2 $\pm$ 5.0	0 – 26.1
AT (%)	42.2 $\pm$ 8.8	29.3 – 53.0
Borg score at peak exercise	6.0 $\pm$ 3.0	1 – 10
Decrease in SaO ₂ at peak exercise (%)	4 $\pm$ 3	-1 – 10

[†] breathing reserve: MVV – V_{emax}

AT: anaerobic threshold; CPET: cardiopulmonary exercise testing;

FEV₁: forced expiratory volume in 1 second; RV: residual volume;

SD: standard deviation; TLC: total lung capacity; VO₂: oxygen uptake;

WR: work rate

maximal tests, the causes of exercise limitation were:

- 1) ventilatory limitation, as defined by V_{emax} greater than 85% of MVV, in 17 patients (59%),
- 2) significant oxygen desaturation of more than 4% at peak exercise compared to baseline values in 1 patient (3%), and
- 3) both ventilatory limitation and oxygen desaturation in 11 patients (38%).

Neither cardiovascular limitation nor serious electrocardiographic abnormality was observed in any of the subjects in this study. Although the exact cause/s of exercise limitation cannot be determined in the 4 patients who performed submaximal tests, interestingly all 4 of these patients complained only of leg fatigue at peak exercise. Anaerobic threshold was attained by 5 out of the 33 patients with a mean AT% of 42.2 (range 29.3 to 53.0). The AT% was low (<40) in 2 of these patients.

Figure 1 shows the relationship between FEV₁ and peak oxygen uptake. Although there was significant correlation ($r = 0.597$, $P = 0.01$) between peak VO₂ percent predicted and FEV₁ percent predicted, there was marked variability of peak VO₂ for a given degree of airflow obstruction. There was no relationship ($r = -0.074$, $P = 0.689$) between peak VO₂ percent predicted and the degree of hyperinflation at rest as determined by the ratio of residual volume to total lung capacity (RV/TLC). Likewise, there was also no significant correlation ($r = 0.292$, $P = 0.118$) between peak VO₂ percent predicted and the ratio of V_{emax} to MVV (V_{emax}/MVV).

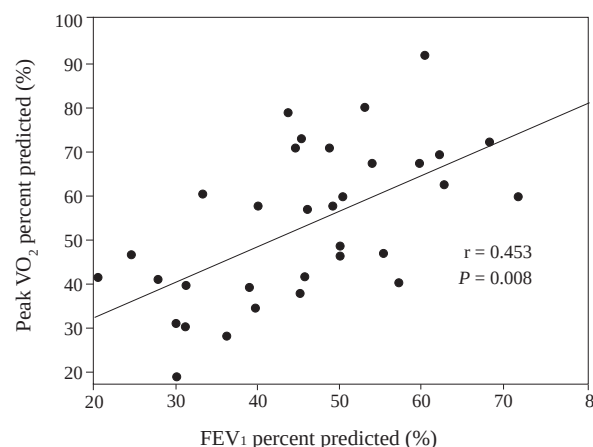


Fig. 1. Correlation between FEV₁ percent predicted and peak VO₂ percent predicted.

Termination of exercise by the supervising physician was not required for any patient and there were no complications arising from the conduct of CPET in any patient.

Discussion

Simple physiologic parameters such as forced expiratory volume have traditionally been used to define the severity of disease processes involving the lung. However, the findings of the present as well as a previous study¹ are that the reduced exercise capacity in COPD patients shows only a moderate relationship with lung function impairment. While there is a relationship between FEV₁ and peak exercise capacity, there is a wide range of exercise performance for a given degree of airflow obstruction (Fig. 1). Basic indices such as FEV₁, therefore, do not adequately characterise the degree of functional impairment that the disease process imposes on the individual. Ultimately, it is the integrated influence of multiple factors e.g., pulmonary mechanics, pulmonary circulation, cardiac, peripheral muscle and psychosocial factors that determine an individual patient's functional level. Various types of exercise testing may serve this integrative role and objectively assess functional outcome in COPD. Commonly used forms of exercise tests for this purpose include six-minute walk testing (6MWT) and maximal CPET. Advantages of the 6MWT include its minimal technical requirements, ease of execution by even severely debilitated patients, good reproducibility, and correlation with maximal exercise testing and functional status questionnaires. Disadvantages include the lack of standardisation in methodology that frequently prevents reliable comparison between centres. In addition, the 6MWT does not easily allow collection of basic physiologic data during exercise which may be used in assessing mechanisms of impairment, response to therapy, or in selecting patients for intervention. The utility of field exercise tests like the 6MWT is also

limited to moderate or severe disease since the walking distance is unlikely to be limited by mild impairment.

There has been little discussion in the literature regarding the criteria that should be used to determine factors that limit exercise tolerance in COPD patients. In this study, we followed the principle that the physiologic function that is limiting exercise is the one that is utilised at maximum capacity at end exercise while all other physiologic functions are operating below maximal capacity.⁹ By conducting CPET and with non-invasive measurements only, we were able to objectively determine that the causes of exercise limitation in the majority of our patients with COPD were secondary to ventilatory abnormalities or oxygen desaturation or both.

An analysis of the symptoms during CPET may also suggest factors which either directly or indirectly contribute to exercise limitation. Dyspnoea and/or leg fatigue were the dominant symptoms at peak exercise among patients in the present study. These symptoms were also the dominant symptoms at peak exercise in previous studies involving patients with chronic airflow limitation (CAL).¹⁰⁻¹² While it is expected and well established that patients with CAL become more breathless than controls during exercise at similar work rates, given the limited ventilatory reserve of these patients, it may be somewhat surprising that many patients with CAL complain mainly of leg fatigue at peak exercise. In the study by Killian et al,¹⁰ as many as 43% of COPD patients experienced leg fatigue as the predominant symptom limiting exercise. The frequency of this complaint in COPD patients during CPET raises a possibility of dysfunction of the limb muscles in these patients. Although this could not be determined objectively, the 4 patients in the present study who did not achieve maximal testing based on the above criteria are quite likely to have limb muscle dysfunction limiting exercise as all of them experienced leg fatigue as the predominant symptom at peak exercise. Limb muscle strength has been found to be often reduced in patients with COPD.^{13,14} In addition, there is evidence for both peripheral muscle wasting¹⁵⁻¹⁷ and a change in muscle fibre type^{18,19} in patients with COPD. Possibly secondary to these structural changes, peripheral muscle metabolic capacity is reduced and low activity of mitochondrial enzymes has also been demonstrated in the lower limb muscles of these patients.²⁰ A recent study using nuclear magnetic resonance showed evidence of abnormal limb muscle metabolism during exercise in patients with CAL.²¹ The exact mechanisms underlying limb muscle dysfunction in patients with COPD are not known, but major possibilities include malnutrition, impaired muscle perfusion, hypoxia, inactivity, medications, loss of muscle mass secondary to ageing and myopathy due to circulating cytokines.^{14,22} Towards this end, CPET can assist in

identifying patients with symptom-limitation suggestive of limb muscle dysfunction so that therapeutic strategies such as exercise training, nutritional intervention or anabolic steroids²³ can be considered.

Metabolic acidosis that develops during exercise in some patients with COPD may be another contributory factor to exercise limitation in these patients by increasing ventilatory demand during exercise. A previous study¹ has demonstrated that the development of metabolic acidosis can be accurately determined non-invasively by using the V-slope method in spite of the ventilatory limitation during exercise in such patients. A low AT during CPET can be considered as indicative of deconditioning in sedentary patients with COPD as compared to active patients who either have normal or unmeasurable AT during CPET.²⁴ In the present study, we were able to determine the AT in 5 patients (15.2%) and identify that the AT was not reached in the rest of the patients by using non-invasive means. In 2 COPD patients who developed metabolic acidosis and have a low AT during CPET, exercise training, based on the benefits accrued from reducing the exercise-induced metabolic acidosis, has the potential to improve exercise tolerance. As it would not have been possible to differentiate these 2 patients from the rest based on exertional symptoms alone, it is therefore necessary to perform CPET for patients with COPD in order to select physically deconditioned patients most likely to benefit from exercise training during pulmonary rehabilitation.

Conclusions

Using non-invasive means only, CPET is able to determine the causes of exercise limitation in the majority of patients with COPD. The causes of exercise limitation in most of the patients in this study were ventilatory abnormalities and/or oxygen desaturation. Limb muscle dysfunction and physical deconditioning may be contributory factors of exercise limitation in some patients. Spirometry and lung volume measurements at rest do not accurately predict exercise capacity in patients with COPD and CPET is useful for accurate determination of maximal exercise capacity in these patients.

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