Respiratory Physiology & Neurobiology 186 (2013) 81–86

Contents lists available at SciVerse ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Differences in gas exchange between severities of chronic obstructive pulmonary disease

Wilawan Thirapatarapong[a,b], Hilary F. Armstrong[a], Byron M. Thomashow[c], Matthew N. Bartels[a,*]

[a] Department of Rehabilitation and Regenerative Medicine, Columbia University Medical Center, New York, NY 10032, USA
[b] Department of Rehabilitation Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
[c] Department of Medicine, Pulmonary, Allergy and Critical Care, Columbia University Medical Center, New York, NY 10032, USA

ARTICLE INFO

Article history:
Received 17 October 2012
Received in revised form
18 December 2012
Accepted 28 December 2012

Keywords:
Gas exchange
Ventilation
Chronic obstructive pulmonary disease
Exercise test

ABSTRACT

Impaired ventilation on cardiopulmonary exercise test (CPET) is seen in patients with chronic obstructive pulmonary disease (COPD). However, evaluation of the differences of abnormal gas exchange in COPD according to GOLD severity criteria is limited. A retrospective review was performed on all COPD patients referred for CPET at our center between 1998 and 2010. There were 548 patients compared according to GOLD severity. GOLD groups were significantly different from each other in regards to pressure of end-tidal carbon dioxide (PET_{CO_2}) with progressively higher PET_{CO_2} with increasing GOLD severity. Ratio of minute ventilation to carbon dioxide production ($\dot{V}E/\dot{V}_{CO_2}$) and exercise capacity as measured by and $\dot{V}_{O_2}$ % and work rate in watts% was inversely proportional to GOLD severity. Breathing reserve, minute ventilation, and tidal volume at peak exercise were significantly decreased with increasing disease severity between GOLD groups. We concluded that gas exchange is distinctive among different GOLD severity groups; specifically, GOLD 3 and 4 have a significantly higher PET_{CO_2} and a significantly lower $\dot{V}E/\dot{V}_{CO_2}$ than GOLD 2.

1. Introduction

Cardiopulmonary exercise testing (CPET) was established as the gold standard to evaluate exercise capacity in patients with severe chronic obstructive pulmonary disease (COPD) (American Thoracic Society, 2003; Spruit et al., 2007) in the National Emphysema Treatment Trial (NETT) (National Emphysema Treatment Trial Group, 2003) which assessed patients for lung volume reduction surgery. CPET is also used to assess exercise intolerance and can demonstrate impaired ventilation in other conditions such as pulmonary hypertension (PH) and interstitial lung disease (Ross and Kathy, 2011).

In normal individuals with exercise, tidal volume (VT) increases, expiratory time decreases, and end expiratory lung volume (EELV) decreases. However, in COPD patients, ventilatory abnormalities can lead to neuromechanical uncoupling as hyperinflation and increased work of breathing effect the mechanics of breathing (Ferrazza et al., 2009), resulting in increased elastic and dynamic work which increases oxygen consumption. This can contribute to impaired ventilation (Hyatt, 1983), altered oxygen consumption and may be exacerbated by concurrent pulmonary vascular disease.

Commonly used noninvasive variables to evaluate ventilation are pressure of end-tidal carbon dioxide (PET_{CO_2}) and ratio of minute ventilation to rate of carbon dioxide production ($\dot{V}E/\dot{V}_{CO_2}$) (American Thoracic Society, 2003; Spruit et al., 2007). Prior studies evaluating CPET in COPD patients have demonstrated a lower PET_{CO_2} with higher $\dot{V}E/\dot{V}_{CO_2}$ at peak exercise than normal individuals (Hansen et al., 2007; Liu et al., 1995; Ofir et al., 2008), reflecting impaired ventilation. However, most studies analyzed patients with mild COPD or tested severe COPD patients on room air, potentially limiting peak exercise.

Although, the cited study (Paoletti et al., 2011) has already reported the differences of $\dot{V}E/\dot{V}_{CO_2}$ and PET_{CO_2} in different severities of pulmonary emphysema, it did not compare outcomes among patients with COPD as ranked by GOLD criteria and the patients with only moderate to severe emphysema were recruited. In addition, there were a relative small number of patients ($n = 16$). The other study (Pinto-Plata et al., 2007) demonstrated a distinct exercise response on CPET among COPD patients classified by the GOLD criteria; however, it did not compare pulmonary gas exchange as measured by $\dot{V}E/\dot{V}_{CO_2}$. Furthermore, this study had a relatively small number of severe patients and a limited number of subjects were able to achieve peak exercise performance.

In order to address some of the limitations, we proposed to assess pulmonary gas exchange with $\dot{V}E/\dot{V}_{CO_2}$ and PET_{CO_2} on CPET,

* Corresponding author at: Unit #38, 630 West 168th Street, New York, NY 10032, USA.
E-mail addresses: wilawan.thi@mahidol.ac.th (W. Thirapatarapong), hfa2104@columbia.edu (H.F. Armstrong), bmt1@columbia.edu (B.M. Thomashow), mnb4@columbia.edu (M.N. Bartels).

1569-9048/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.resp.2012.12.013

performed on supplemental oxygen as needed in order to maximize capacity to truly evaluate ventilatory changes in various severities of COPD patients as rated by the GOLD criteria. Our study is designed in a large group of patient with COPD and includes the patients with different GOLD severity. The primary hypothesis is that ventilation is distinctive among COPD patients with various severities and this study supports and adds to the prior studies by bridging some of gaps and adding a strong confirmatory voice to those findings.

2. Methods

2.1. Study subjects

We performed a retrospective chart review of all patients with COPD referred for CPET to the Center for Chest Disease at the New York Presbyterian Hospital, Columbia University Medical Center between January 1998 and June 2010. Patients were referred for exercise tests as part of their standard clinical evaluation for transplant, lung volume reduction surgery, pulmonary rehabilitation program, or clinical management. Selection of patients was based on the following criteria: (1) clinical diagnosis of COPD (GOLD criteria) and (2) CPET and pulmonary function test (PFT) performed within 4 months of each other. Exclusion criteria consisted of patients with prior major pulmonary surgery, congestive heart failure, or recent myocardial infarction. The Institutional Review Board of Columbia University Medical Center approved this study.

2.2. Pulmonary function testing

All pulmonary function tests (PFT) were performed according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (Celli et al., 2004) and were performed before and 20–30 min after short-acting bronchodilation with albuterol. The values reported include the post-bronchodilator values of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC), and residual volume (RV). Percent of predicted PFTs was calculated for males and females as described in the prior publications (Capro et al., 1981, 1982; Capro and Morris, 1981). Based on ATS/ERS GOLD criteria, the patients were divided into the following four stages as long as they had FEV_1/FVC ratio < 0.7: GOLD 1 (mild disease) – $FEV_1 \geq 80\%$ predicted; GOLD 2 (moderate disease) – $FEV_1 < 80\%$ and $\geq 50\%$ predicted; GOLD 3 (severe disease) – $FEV_1 < 50\%$ and $\geq 30\%$ predicted; and GOLD 4 (very severe disease) – $FEV_1 < 30\%$ predicted (Vestbo et al., 2012).

2.3. Cardiopulmonary exercise testing

CPET was performed on an electronically braked cycle ergometer (Ergometrics 800, SensorMedics Inc, Yorba Linda, CA) with an Encore metabolic cart from 2005 to 2011; Vmax 229 series workstation before 2005 (SensorMedics Inc., Yorba Linda, CA). Continuous 12-lead telemetry was monitored via CardioSoft electrocardiogram software from 2005 to 2011 (GE/CardioSoft, Houston, TX); Max-1 electrocardiogram before 2005 (Marquette Medical Systems, Milwaukee, WI). Oxygen saturation (SpO_2) was recorded with a N595 pulse oximeter from 2005 to 2011 (Nellcor, Boulder, CO); Sat-Trak Monitor before 2005 (SensorMedics Inc., Yorba Linda, CA). CPETs were performed with 5 min baseline; 3 min unloaded cycling; symptom-limited exercise by 5 or 10 W/min ramp protocol based on maximal voluntary ventilation (MVV) by NETT criteria (National Emphysema Treatment Trial Group, 2003). Patients still took their usual medications on the day of the CPET, including short acting bronchodilators within 2 h of the test. They were tested on $30.0 \pm 0.2\%$ supplemental oxygen if they were prescribed oxygen in order to maintain normoxia during exercise, both for safety reasons and for achieving a more accurate measurement of the patients' exercise capacity. Supplemental oxygen was delivered via a closed system and titrated breath by breath to maintain the target inspired oxygen level. CPET variables were collected breath by breath and included rate of carbon dioxide production ($\dot{V}_{CO_2}$), maximal workload (peak watts) and watts percent predicted (watts%), oxygen consumption by weight ($\dot{V}_{O_2}$ in mL/kg/min), percent of predicted oxygen consumption ($\dot{V}_{O_2}$%), minute ventilation ($\dot{V}E$), VT, respiratory rate, PET_{CO_2}, heart rate at baseline and peak exercise (HR_{rest} and HR_{peak}), systolic blood pressure at baseline and peak exercise (SBP_{rest} and SBP_{peak}) and diastolic blood pressure at baseline and peak exercise (DBP_{rest} and DBP_{peak}). Calculation was made of ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}_{CO_2}$). In the majority of the COPD patients studied, the anaerobic threshold (AT) could not be identified, therefore values of exercise variables measured at AT are not provided. $\dot{V}E/\dot{V}_{CO_2}$ peak was defined as the $\dot{V}E/\dot{V}_{CO_2}$ at peak exercise. Age predicted peak HR was calculated using $208–0.7 \times$ age (Tanaka et al., 2001). The predicted watts and $\dot{V}_{O_2}$ were calculated for males and females as described by Jones et al. (1985).

Table 1
Characteristics and PFT variables among GOLD groups.

Characteristics and PFT	GOLD 2 $n=50$	GOLD 3 $n=129$	GOLD 4 $n=369$
Age (years)	66 ± 12	65 ± 10	$61 \pm 8^{b,c}$
% Female	46%	51%	50%
BMI (kg/m^2)	28.1 ± 5.1	26.6 ± 5.1	$24.8 \pm 5.1^{b,c}$
FEV_1 (% predicted)	61 ± 9	38 ± 6^{a}	$20 \pm 5^{b,c}$
FVC (% predicted)	83 ± 12	71 ± 12^{a}	$49 \pm 13^{b,c}$
TLC (% predicted)	92 ± 22	105 ± 16^{a}	$119 \pm 18^{b,c}$
RV (% predicted)	107 ± 40	148 ± 36^{a}	$225 \pm 57^{b,c}$
D_{LCO} (% predicted)	44 ± 18	$37 \pm 14^{a*}$	$30 \pm 12^{b,c}$

Data are presented as mean ± SD, unless otherwise indicated. BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lung for carbon monoxide.

[a] Significantly different between GOLD 2 and GOLD 3.
[b] Significantly different between GOLD 2 and GOLD 4.
[c] Significantly different between GOLD 3 and GOLD 4.

2.4. Statistical analysis

Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL) and are presented as mean ± standard deviation. Categorical variables were compared with a chi-square test. One-way analysis of variance was used to compare variables between different GOLD groups. The Gabriel post hoc test was used to compare groups of different sizes. Between groups comparisons for those on and off of supplemental oxygen and for female and male were performed using *t*-tests for independent samples. Between groups comparisons for those on and off of supplemental oxygen were performed using *t*-tests for independent samples. Statistical significance was set at $p \leq 0.05$ and 95% confidence intervals were determined.

3. Results

A total of 556 patients met the inclusion criteria. There were 8, 50, 129, and 369 patients from GOLD 1 to GOLD 4, respectively. Because the relative small numbers of GOLD 1 subjects, no differences were seen between GOLD 1 and 2 in regards to any CPET variables (data not shown), and it has been already reported that patients in GOLD 1 have CPET values similar to those of control subjects, GOLD 1 group was not included in the statistical analysis.

Table 1 shows the baseline characteristics and PFTs by GOLD criteria. Mean FEV_1%, FVC%, and percentage of diffusing capacity of the lung for carbon monoxide (D_{LCO}%) significantly decreased