Respiratory Physiology & Neurobiology 197 (2014) 9–14

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

Excess ventilation and ventilatory constraints during exercise in patients with chronic obstructive pulmonary disease

Elisabetta Teopompi, Panagiota Tzani, Marina Aiello, Maria Rosaria Gioia, Emilio Marangio, Alfredo Chetta*

Respiratory Disease and Lung Function Unit, Department of Clinical and Experimental Medicine, University of Parma, Italy

ARTICLE INFO

Article history:
Accepted 7 March 2014
Available online 19 March 2014

Keywords:
COPD
Exercise
Ventilatory response

ABSTRACT

We assessed the relationship between minute ventilation/carbon dioxide output (VE/VCO_2) and ventilatory constraints during an incremental cardiopulmonary exercise testing (CPET) in patients with chronic obstructive pulmonary disease (COPD).

Slope and intercept of the VE/VCO_2 linear relationship, the ratios of inspiratory capacity/total lung capacity (IC/TLC) and of tidal volume (VT) over vital capacity (VT_{peak}/VC) and IC (VT_{peak}/IC) and over forced expiratory volume at 1st second (VT_{peak}/FEV_1) at peak of exercise were measured in 52 COPD patients during a CPET. The difference peak-rest in end-tidal pressure of CO_2 ($PETCO_2$) was also measured.

VE/VCO_2 intercept showed a negative correlation with IC/TLC peak ($p < 0.01$) and a positive one with VT_{peak}/FEV_1 ($p < 0.01$) and with $PETCO_2$ peak-rest ($p < 0.01$). VE/VCO_2 slope was negatively related to VT_{peak}/VC, VT_{peak}/IC and VT_{peak}/FEV_1 (all correlations $p < 0.05$) and to $PETCO_2$ peak-rest ($p < 0.01$).

In COPD, VE/VCO_2 slope and intercept provide complementary information on the ventilatory limitation to exercise, as assessed by changes in the end-expiratory lung volume and in tidal volume excursion.

1. Introduction

An excess in exercise ventilation for a given metabolic rate may occur in patients with chronic obstructive pulmonary disease (COPD). The minute ventilation (VE) to the carbon dioxide output (VCO_2) ratio, also known as ventilatory equivalent for CO_2 (VE/VCO_2) (Wasserman et al., 1994), may be increased in patients with COPD during exercise, as compared to control subjects (O'Donnell et al., 2001; Paoletti et al., 2011). In addition, in COPD patients the slope of the VE/VCO_2 linear relationship was found to be negatively related to the peak oxygen uptake (VO_2peak) during a rapidly incremental cardiopulmonary exercise testing (CPET) (Caviedes et al., 2012; Teopompi et al., 2013). Interestingly, the VE/VCO_2 slope values were found to be decreased in patients with more severe emphysema, by indicating a relationship between VE/VCO_2 slope and ventilatory limitation (Paoletti et al., 2011). Furthermore, even the intercept of the VE/VCO_2 relationship has the potential for understanding the ventilatory response to exercise in patients with chronic cardiopulmonary disabling conditions (Agostoni et al., 2011; Teopompi et al., 2013).

Patients with COPD experience ventilatory constraints on exertion. In these patients, the development of dynamic hyperinflation limits exercise capacity and plays a key role in the perception of exertional breathlessness (O'Donnell, 2008). Indeed, COPD patients while exercising, may breathe in before achieving a full exhalation and, accordingly, trap air within the lungs with each further breath with serious mechanical and sensory consequences. Notably, dynamic lung hyperinflation may progressively restrict the tidal volume excursion and exercise ventilation can increase only by quickening the breathing frequency, thereby inducing a further hyperinflation in a vicious circle. Furthermore, in COPD patients dynamic hyperinflation may be associated with a poor cardiovascular response to exercise (Tzani et al., 2011).

Up to now, no study has been specifically aimed to assess the relationship between the excess in exercise ventilation for a given metabolic rate and the ventilatory limitation in COPD patients. The

Abbreviations: AT, anaerobic threshold; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in 1st second; FVC, forced vital capacity; IC, inspiratory capacity; RER, respiratory exchange ratio; SD, standard deviation; SpO_2, oxygen saturation; TLC, total lung capacity; TLco, lung diffusion capacity for carbon monoxide; VC, vital capacity; VCO_2, carbon dioxide production; VE, minute ventilation; VE/VCO_2, ventilatory equivalent for CO_2; VO_2, oxygen uptake; VT, tidal volume.

* Corresponding author at: Unità di Malattie Respiratorie e Funzionalità Polmonare, Università di Parma, Padiglione Rasori, via G. Rasori 10, 43100 Parma, Italy. Tel.: +39 0521 703475; fax: +39 0521 292615.
E-mail address: chetta@unipr.it (A. Chetta).

http://dx.doi.org/10.1016/j.resp.2014.03.002
1569-9048/

aim of the present study was, therefore, to measure in a cohort of COPD patients the VE/VCO_2 value, both in terms of slope and in terms of intercept, and to ascertain whether or not these parameters may be related to the development of dynamic hyperinflation and to the tidal volume constraints. We hypothesized that the VE/VCO_2 slope and intercept values might be differently associated to the ventilatory constraints during exercise in COPD patients.

2. Methods

2.1. Patients

We consecutively enrolled over a 9-month period, from January 2013 to September 2013, patients affected by COPD, who were admitted to a pulmonary rehabilitation program. COPD was diagnosed according to the GOLD criteria (Pauwels et al., 2001) and patients with moderate to severe airflow obstruction, i.e. forced expiratory volume in 1 s/vital capacity ratio (FEV_1/VC) < 70% and $FEV_1 \leq 80\%$ of predicted value, were included. Eligibility criteria of patients were (1) ex-smoking habit; (2) no long-term oxygen therapy; (3) BMI ≥ 20 and ≤30 kg/m^2; (4) stable clinical condition for at least 6 weeks; (5) absence of any comorbidity affecting exercise performance (anemia, chronic heart failure, neuromuscular disorders, or malignancies); (6) no other concomitant chronic respiratory disease, such as asthma or pulmonary fibrosis; (7) ability to perform a CPET with a peak of respiratory exchange ratio (RER) ≥ 1.05 in order to exclude poor motivation (American Thoracic Society, 2003); (8) CPET stopped for muscle fatigue and/or dyspnea. To be included, patients were considered as former smokers when they were abstinent from smoking from at least six months.

Patients were not pretreated with beta$_2$-agonists before exercise testing, but were allowed to continue with their regular therapy during the study. All the procedures and their risks were explained to the patients, who gave their written informed consent to enter the study, which was conducted according to the Declaration of Helsinki. The protocol was approved by the ethical committee of the University Hospital of Parma. All participants' data were analyzed and reported anonymously.

2.2. Lung function

Pulmonary function tests were performed according to international recommendations (Miller et al., 2005; Wanger et al., 2005). A flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (Vmax 22 and 6200, Sensor Medics, Yorba Linda, U.S.A.) were used for the measurements. VC, forced vital capacity (FVC), FEV_1 and forced expiratory flow at 50% of FVC (FEF_{50} in L/s) and forced inspiratory flow at 50% of FVC (FIF_{50} in L/s) were recorded. FEV_1/VC and FEF_{50}/FIF_{50} ratios were taken as indices of airflow obstruction and airway collapsibility, respectively.

Thoracic gas volume (TGV) was measured by body plethysmography with the subject panting against a closed shutter at a frequency slightly <1 Hz and their cheeks supported by their hands. Total lung capacity (TLC) was obtained as the sum of TGV and linked inspiratory capacity (IC). IC/TLC ratio was taken as index of hyperinflation of the lung. At least three measurements were made for each spirometry and lung volume variable to ensure reproducibility and the highest value was used in subsequent calculations. The flow-sensor was calibrated before each test using a three-liter syringe. Lung diffusion capacity for carbon monoxide (TLco) was measured by the single breath method using a mixture of carbon monoxide and methane; this measurement was done at least in duplicate. TLC, VC, IC, FEV1 and TLco were expressed as a percentage of the predicted values, which were obtained from regression equations (Quanjer et al., 1993; Cotes et al., 1993).

2.3. Cardiopulmonary exercise test

CPET was performed according to a standardized procedure (American Thoracic Society, 2003). Patients were not pretreated with beta$_2$-agonists before testing, but were allowed to take their current therapy. After calibrating the oxygen and carbon dioxide analyzers and flow mass sensor, patients were asked to sit on an electromagnetically braked cycle ergometer (Corival PB, Lobe Bv, Groningen, The Netherlands) and the saddle was adjusted properly to avoid the maximal extension of the knee. The exercise protocol involved an initial 3 min of rest, followed by unloaded cycling for another 3 min with an increment every minute of 5–15 W, according to the patient's anthropometry and degree of functional impairment, in order to achieve an exercise time in between 8 and 12 min. Patients were asked to maintain a pedaling frequency of 60 rpm indicated by a digital display placed on the monitor of the ergometer.

Breath-by-breath oxygen uptake (VO_2 in L/min), carbon dioxide production (VCO_2 in L/min), tidal volume (VT in L) and minute ventilation (VE in L/min) were recorded during the test (CPX/D; Med Graphics, St. Paul, MN, U.S.A.). Patients were continuously monitored by a 12-lead electrocardiogram (Welch Allyn CardioPerfect, Delft, The Netherlands) and a pulse oximeter (Pulse Oximeter 8600, Nonin Medical Inc., MPLS, MN, U.S.A.). Blood pressure was measured at 2 min intervals. Exercise was stopped when at least one of the following criteria was reached: (1) symptoms such as unsustainable dyspnea, leg fatigue or chest pain, (2) RER > 1.15, (3) peak workload > 80% predicted, (4) peak VO_2 > 84% predicted, 5) peak heart rate > 90% predicted, (6) ventilatory reserve < 15%, (7) ECG significant ST-segment depression, (8) drop in systolic blood pressure or oxygen saturation (SpO_2) ≤ 84 (American Thoracic Society, 2003). Predicted values were calculated according to equations by Wasserman et al. (Wasserman et al., 1994).

Peak workload and peak VO_2 were recorded as the mean value of watts and VO_2 during the last 20 s of the test. Peak VO_2 was expressed as absolute value in mL/kg/min. Anaerobic threshold (AT) was non-invasively determined by both V-slope and ventilatory equivalents methods ("dual method approach"), as the respiratory exchange ratio approximated 1.0 (American Thoracic Society, 2003), and was expressed as absolute value in mL/min. The AT was determined by two non-blinded physicians (ET and PT) attending to the CPET.

The ventilatory response during exercise was expressed as a linear regression function by plotting VE against VCO_2 obtained every 10 s, excluding data above the ventilatory compensation point (American Thoracic Society, 2003). Then, the slope and *Y* intercept values were obtained from the VE/VCO_2 regression line. The end-tidal pressure of CO_2 ($PETCO_2$, in mmHg) was measured as mean of $PETCO_2$ during the 3-min rest period and during the last 20 s of the test and was recorded as the difference between $PETCO_2$ peak and $PETCO_2$ rest ($PETCO_2$ peak-rest).

Changes in operational lung volumes were assessed every two min during exercise and at peak exercise, taking the IC measured at rest, as the baseline. After a full explanation to each patient of the procedure, satisfactory technique and reproducibility of IC maneuvers were established during an initial practice session at rest. Assuming that TLC remains constant during exercise in COPD (Stubbing et al., 1980), changes in IC reflect changes in end-expiratory lung volume. Accordingly, dynamic hyperinflation may be defined as a decline in the IC greater than zero. According to IC/TLC ratio at peak of exercise, patients were divided in two categories: patients with IC/TLC ≤ 0.25 or >0.25. The patients with the