Association between inspiratory muscle weakness and slowed oxygen uptake kinetics in patients with chronic obstructive pulmonary disease

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Association between inspiratory muscle weakness and slowed oxygen uptake kinetics in patients with chronic obstructive pulmonary disease

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Running Head: Inspiratory weakness in patients with COPD

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Abstract

INTRODUCTION: Patients with chronic obstructive pulmonary disease (COPD) may have poor inspiratory muscle function, which reduces minute and alveolar ventilation, leading to increased hypoxemia and slow pulmonary oxygen uptake ($\dot{V}O_2$) kinetics. However, little is known about the effect of inspiratory muscle weakness (IMW) on oxygen uptake kinetics in patients with COPD. Thus, we tested the hypothesis that COPD patients with IMW have slowed $\dot{V}O_2$ kinetics. **METHODS:** An observational study was conducted including COPD patients with moderate to severe airflow limitation and a history of intolerance to exercise. Participants were divided into two groups: (IMW+; n = 22) (IMW-; n = 23) of muscle weakness. **RESULTS:** Maximal inspiratory ($P_{I_{max}}$), maximal expiratory ($P_{E_{max}}$), maximal sustained inspiratory ($P_{I_{max_{sustained}}}$), and maximal endurance inspiratory muscle strength were lower in IMW+ patients (36 ± 9.5 cmH₂O; 52 ± 14 cmH₂O; 20 ± 6.5 cmH₂O; 94 ± 84 s, respectively) than in IMW- patients (88 ± 12 cmH₂O; 97 ± 28 cmH₂O; 82.5 ± 54 cmH₂O; 559 ± 92 s, respectively; $p < 0.05$). Moreover, the six-minute walk test and peak $\dot{V}O_2$ were reduced in the IMW+ patients. During the constant work test, $\dot{V}O_2$ kinetics were slowed in the IMW+ compared to IMW- patients (88 ± 29 vs 61 ± 18 s, $p < 0.05$). **CONCLUSION:** Our findings demonstrate that inspiratory muscle weakness in COPD is associated with slowed $\dot{V}O_2$ kinetics, and thus, reduced functional capacity.

Keywords: Inspiratory muscle weakness, exercise, oxygen uptake, respiratory muscle, intolerance

Introduction

Previous studies have demonstrated a slowed dynamic increase in pulmonary oxygen uptake ($\dot{V}O_{2P}$) in patients with chronic obstructive pulmonary disease (COPD) (Nery et al. 1982; Palange et al. 1995; Chiappa et al. 2008). Patients with COPD typically experience locomotor muscle fatigue as a result of pulmonary system limitations (Amann et al. 2010); systemic and peripheral O_2 delivery may be reduced, leading to slowed $\dot{V}O_2$ kinetics, which become limited by the availability of O_2 (Chiappa et al. 2008). Moreover, lung hyperinflation secondary to underlying lung disease can overload the respiratory muscles, leading to reduced muscle blood flow. This, in turn, results in muscular weakness and fatigue, and increases the recruitment of accessory inspiration muscles, contributing to exercise intolerance (Polkey et al. 1996; Amann et al. 2010; ; Chiappa et al. 2014; Vieira et al. 2014).

Recent studies have shown that inspiratory muscle changes affect peripheral skeletal muscles (Gosselink et al. 1996; Borghi-Silva et al. 2008; Gosselink et al. 2011; Chiappa et al. 2014). For example, a previous study in healthy individuals demonstrated an inverse correlation between changes in respiratory work and blood flow to locomotor muscles, at maximal aerobic capacity (Harms et al. 1997), which may lead to exacerbation of dyspnea and contribute to exercise intolerance. However, impaired respiratory muscle dysfunction may also be implicated in impaired exercise performance, commonly observed in patients with COPD (Singer et al. 2011). There is currently a lack of information on the association between inspiratory muscle strength and slowed $\dot{V}O_2$ kinetics observed in patients with moderate to severe COPD. Thus, we tested the hypothesis that slowed $\dot{V}O_2$ kinetics, commonly observed in COPD patients (Chiappa et

al. 2008), are associated with inspiratory muscle weakness and reduced minute ventilation (Poole and Jones 2012).

Materials and Methods

Patients and Study Design

A cross-sectional study was conducted including patients with a previous diagnosis of COPD based on the criteria of the Global Initiative Rating for Chronic Obstructive Lung Disease - GOLD (Vestbo et al. 2013). Patients were included in the study if they 1) were diagnosed with COPD (GOLD) with $FEV_1 < 40\%$ of predicted (Vestbo et al. 2013); 2) had self-reported dyspnea and/or fatigue during at least one activity of daily living (based on the 6-20 Borg Category-Ratio Scale (CRS) (Wilson and Jones 1989); and 3) were able to adequately perform the $P_{I_{max}}$ and $P_{E_{max}}$ tests. Patients were excluded from the study if they 1) were engaged in any pulmonary rehabilitation program; 2) had a cough or any sputum production, for at least three consecutive months in the previous two years, consistent with a diagnosis of chronic bronchitis (Menezes et al. 1994); 3) had a severe or very severe air flow limitation ($FEV_1 < 30\%$ of predicted); 4) had a history of intolerance to exercise (distance traveled on the Six-Minute Walk Test [6MWT] < 350 m; (Guyatt et al. 1985); 5) had a musculoskeletal or neurological condition, that might affect their exercise performance, symptomatic heart disease, or had received previous pulmonary surgery, 6) had experienced acute exacerbation of their COPD requiring a change in pharmacological management within the previous two months; 7) were taking oral corticosteroids; 8) had changed their medication

dosage within the previous 12 weeks in the absence of acute exacerbation; or 9) had experienced heart failure.

Before enrollment into the study, patients' lung function was optimized using long-acting bronchodilators and corticosteroids and, if needed, patients could use short-acting bronchodilators to optimize their performance or as a rescue therapy (120 µg of salbutamol/20 µg of ipratropium, Combivent Boehringer Ingelheim GmbH, Ingelheim, Germany). The procedures and potential risks were explained to patients in detail. This study was conducted in compliance with the Declaration of Helsinki and received approval from the Human Research Ethics Committee, University Center of Serra Gaúcha, Caxias do Sul, Brazil. Written informed consent was provided by each participant.

Procedures

After screening, participants were allocated into one of two groups according to either the presence or absence of inspiratory muscle weakness (IMW+ or IMW-, respectively; Figure 1). At their first visit, participants performed skeletal respiratory muscle strength tests, lung function tests and the six-minute walk test (6-MWT). At their second visit, incremental cardiopulmonary exercise testing was performed along with tests of handgrip strength and endurance. At their third visit, the constant work rate exercise test was performed to measure $\dot{V}O_2$ kinetics. During all phases of the study, Peripheral oxygen saturation (SpO₂) was measured continuously in all patients.

Skeletal Muscle Function

First, handgrip strength was evaluated by measuring the maximum voluntary contraction (MVC). Second, static handgrip endurance was evaluated, in the dominant arm, by performing an exercise at an intensity of 30% MVC for 3 min.

Respiratory Muscle Function

Inspiratory and expiratory muscle function testing was performed using a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil) connected to a system with two unidirectional valves (DHD Inspiratory Muscle Trainer, Chicago, Illinois, USA; (Dall'Ago et al. 2006). A hole, measuring 2 mm in diameter, was used to keep the glottis open and avoid an increase in pressure due to contraction of the facial muscles (Black and Hyatt 1969; ; Tzelepis et al. 1994a; Tzelepis et al. 1994b; Dall'Ago et al. 2006). After two normal tidal breaths, the participant slowly exhaled to a lung volume close to the residual volume, and then performed maximum inspiration against the occluded circuit. PE_{max} were performed after deep inspiration and Total Lung Capacity (TLC) was reached. To measure PI_{max} and PE_{max} , the patients were instructed to sit and use a nose clip (Black and Hyatt 1969; Leech et al. 1983). The test was repeated six times to mitigate the learning effect, with a one-minute interval between each attempt. The greatest single value of PI_{max} and PE_{max} were recorded, where the difference between the two best efforts was no greater than 10% (Nava et al. 1993). PI_{max} and PE_{max} were verified via direct visualization. Predicted values were corrected for age, sex, and weight (Neder et al. 1999). Inspiratory muscle weakness was defined as a PI_{max} value below 60 cm H₂O (Lotters et al. 2002).

Inspiratory Muscle Incremental and Endurance Test

An inspiratory muscle incremental endurance test was performed, in which the patients breathed continuously through a mouthpiece connected to a threshold inspiratory muscle trainer. First, a resistance generating device (K5 POWER breathe, United Kingdom) was used with an initial load of 50% PI_{max} , and loads of 10% PI_{max} were added incrementally every 3 minutes until the patient was unable to continue breathing (Dall'Ago et al. 2006). The maximum inspiratory pressure that the subject could sustain for at least 1 minute (P_{thmax}) was recorded and the P_{thmax}/PI_{max} ratio was calculated, and used as an indicator of inspiratory muscle performance.

Second, the patient breathed against a constant inspiratory sub-maximum load, equivalent to 80% P_{thmax} , and the time-to-task-failure was recorded, and used as an indicator of inspiratory muscle endurance time ((Ribeiro et al. 2006).

Six-Minute Walk Test

The maximum distance covered during the 6-MWT was used as an indicator of sub-maximal functional capacity (Guyatt et al. 1985; ATS Committee 2002; Hernandez et al. 2011). The test was performed on a 25-m course without supplemental additional oxygen but with verbal encouragement, in accordance with the American Thoracic Society Guidelines ATS 2002; (ATS Committee 2002). Respiratory rate, heart rate, pulse oximetry, and blood pressure were monitored during and after the test. Dyspnea was determined using the 6-20 Borg category-ratio scale (Wilson and Jones 1989). The distance walked was measured and expressed as a percentage of the predicted value (Enright and Sherrill 1998; Enright et al. 1998).

Lung Function Test

Spirometry was performed at rest and after inhalation of salbutamol (400 g). Participants performed at least three acceptable expiratory maneuvers. As recommended by the American Thoracic Society (Miller et al. 2005), forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and FEV₁/FVC were measured (Koko PFT, Nspire Health, USA). Benchmarks, approved by the European Respiratory Society, were used for the analysis of FVC, FEV₁, and inspiratory capacity (IC; (Wanger et al. 2005).

Cardiopulmonary Exercise Testing

All participants performed a symptom-limited cardiopulmonary exercise test on an exercise bike (IMBRAMED 10200, Porto Alegre, Brazil). Participants began by resting on the ergometer for 5 to 10 minutes to allow gas exchange measurements to stabilize. Participants then began unloaded cycling for two minutes, after which the work rate was increased by 5 or 10 W every two minutes until their limit of tolerance was reached. Selection of incremental level was achieved according to patient's level of tolerance, with lower levels for patients with more impaired lung function, and higher levels for patients with less impaired lung function. In this way, we guaranteed a minimum exercise time of between 8 to 12 minutes.

Twelve-lead electrocardiographic tracings were obtained every minute (Nihon Khoden Corp., Tokyo, Japan). Blood pressure was measured every two minutes with a standard cuff sphygmomanometer. Expired gases were quantified with aliquots 10 s average using a computerized gas analyzer (Cortex Metalyzer, 2B system, Leipzig, Germany). Although our system was breath-by-breath, the calculation of $\dot{V}O_2$ average every 10 s enabled analysis and graph construction of $\dot{V}O_2$ kinetics. Peak oxygen uptake ($\dot{V}O_{2\max}$)

O₂peak) was expressed as a percentage, predicted according to age, sex, and weight, as per Hansen et al (Hansen et al. 1984). The gas exchange threshold (GET) is defined as the breakpoint in the breath-by-breath values of carbon dioxide output ($\dot{V}\text{CO}_2$) plotted against oxygen uptake ($\dot{V}\text{O}_2$), caused by an increase in $\dot{V}\text{CO}_2$ from bicarbonate buffering of lactic acid (Beaver et al. 1986a). The $\dot{V}\text{O}_2$ at the GET was estimated by the gas exchange method, by visually inspecting the inflection point of $\dot{V}\text{CO}_2$ with respect to $\dot{V}\text{O}_2$ (modified V-slope; (Beaver et al. 1986b), and ventilatory method, when $\dot{V}\text{E}/\dot{V}\text{O}_2$ and expired oxygen pressure ($P_{\text{ET}}\text{O}_2$) increases while $\dot{V}\text{E}/\dot{V}\text{CO}_2$ and expired carbon dioxide pressure ($P_{\text{ET}}\text{CO}_2$) remain stable. For accurate identification of the GET, two regions were discarded from the analysis: 1) the initial 2 min—during which Respiratory Quotient (R) decreases—to account for the effects of transient CO₂ storage, and 2) the points beyond the respiratory compensation point. The reading was performed independently by two experienced observers, without knowledge of the other results or subject identities. The alveolar ventilation (AV) was calculated by the following formula:

$$AV = \dot{V}_E (1 - V_D / [V_T]). \quad \text{Eq. (1)}$$

Where V_D / V_T is the dead space to tidal volume ratio.

The V_D / V_T measurement was calculated from the PaCO₂ values, obtained from the following equation:

$$V_D / V_T = 1 - [863 / \text{PaCO}_2 (m + c / \dot{V}\text{CO}_2)] \quad \text{Eq. (2)}$$

where m and c are the slope and $\dot{V}\text{E}$ -intercept of the $\dot{V}\text{E} - \dot{V}\text{CO}_2$ relationship, respectively. The PaCO₂ value was obtained through an arterial blood gas analysis, with arterial blood obtained via a single radial artery puncture, at three different times of test in rest, middle and end (ATS and ACCP 2003; Ward 2007). Oxygen pulse at peak

exercise was calculated from the ratio of $\dot{V}O_2$ and Heart Rate (HR) at peak and used as an index of stroke volume (Montes de Oca et al. 1996; Benditt et al. 1997; Cordova et al. 1997; Stammberger et al. 1998; Laukkanen et al. 2006; Travers et al. 2007; Vassaux et al. 2008; Come et al. 2012).

Constant Work Rate Test. The difference between $\dot{V}O_{2p}$ at the GET ($\dot{V}O_{2p}$ GET) and $\dot{V}O_{2p}$ at peak exercise ($\dot{V}O_{2p}$ peak; $\Delta\dot{V}O_{2p}$ peak-GET) were determined from the ramp test, performed on an electromagnetically-braked cycle ergometer (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany). Subjects performed constant work rate exercise at 80% $\Delta\dot{V}O_{2p}$ peak-GET (~80% peak incremental work rate) initiated from a baseline of unloaded pedaling, as described elsewhere (Chiappa et al. 2008). Subjects were instructed to maintain a constant pedaling cadence until a tolerable duration was reached (Tlim, min). Oxygen uptake ($\dot{V}O_2$, mL/min), carbon dioxide output ($\dot{V}CO_2$, mL/min), and minute ventilation ($\dot{V}E$, L/min) were measured breath-by-breath using a computer-based system. Gas exchange, ventilatory and cardiovascular variables were averaged every 5 s. $\dot{V}O_{2peak}$ was defined as the greatest value achieved during the test. Heart rate (HR, bpm) was determined using the R-R interval from a 3-lead electrocardiogram. Subjects were asked to rate their 'shortness of breath' at exercise cessation using the 6-20 Borg's CRS.

Kinetics Analysis. The breath-by-breath $\dot{V}O_2$ data was interpolated second-by-second, prior to kinetic analysis (SigmaPlot 11.0, Systat Software, San Jose, CA). The $\dot{V}O_2$ responses to exercise intensity were characterized by the presence of a slow component (Poole et al. 1988; Gaesser and Poole 1996; Chiappa et al. 2008; Jones et al. 2011).

Identification of the point of onset, or emergence, of a slow component is difficult, yielding low confidence intervals for the resulting parameter (time delay slow component, TD_{sc}). However, for conditions where the TD_{sc} is less than 3 – 4 x the “true” time constant of the primary component, the time constant (τ_p) resulting from nonlinear regression analysis will be largely influenced by the TD_{sc} value (Chiappa et al. 2008). Identification of the point of onset or emergence of the slow component involves ensemble-averaging several transitions. Since we used data from a single transition, we opted to fit $\dot{V}O_{2p}$ data from 60 s of baseline pedaling into 180 s, after the onset of exercise. Using this approach, we assured that the same amount of data was included in the kinetic analysis of the primary $\dot{V}O_2$ component for each subject, minimizing the model-dependent effects in our results. The model used for fitting the kinetic response of $\dot{V}O_{2p}$ was

$$[Y]_{(t)} = [Y]_{(b)} + A_p \cdot (1 - e^{-(t - TD_p) / \tau_p}) \quad \text{Eq. (3)}$$

Subscripts *b* and *p* refer the baseline unloaded cycling and primary components, respectively; A_p , TD_p , and τ_p are the amplitude, time delay and time constants, of the exponential response of interest, respectively. The overall kinetics of $\dot{V}O_2$ (~ time to reach 63% of the response following the onset of exercise) was determined by the mean response time ($MRT = \tau + TD$; (Gurd et al. 2005).

Data analysis

The data are expressed as means $\pm$ standard deviations (SD), and all analyses were performed using the SigmaPlot software program (SigmaPlot 11.0, Richmond, USA). One-way analysis of variance (ANOVA) was used to compare the baseline differences between groups. Posthoc analyses were performed with Scheffe’s test, where

appropriate. Pearson's product-moment correlation coefficients were used to assess the level of association between continuous variables. A z-test was used to determine if the amplitude of the slow component of $\dot{V}O_2$ peak was significantly different from zero. The level of statistical significance was set at $p < 0.05$ for all tests.

Results

Between August and December 2014, 50 patients with COPD were screened for inclusion in the study. Five patients did not meet the eligibility criteria (4 did not complete study, and 1 had arrhythmia). Thus, 45 patients were allocated to the two groups; 22 patients were allocated to the IMW+ group and 23 patients were allocated to the IMW- group (Figure 1).

The demographic and spirometric characteristics of the two groups were similar (Table 1), except that IMW+ patients had lower respiratory muscle and handgrip strength, and lower respiratory muscle endurance.

Table 2 shows the outcomes of the 6-MWT, incremental exercise test, and constant work rate exercise test. The IMW+ patients had lower 6-MWT and 6-MWT/Borg CRS values than the IMW- patients ($p < 0.05$). $\dot{V}O_2$ peak was significantly lower in the IMW+ patients compared to the IMW- patients (1170 ± 210 vs. 1823 ± 360 mL/min, $p < 0.05$). $\dot{V}O_2$ /HR was significantly lower in the IMW+ patients compared to the IMW- patients ($p < 0.05$). During the constant work test, the IMW- patients attained a lower time constant (τ) and MRT compared to the IMW+ patients ($p < 0.05$; Figure 2). No significant between-group differences were found with respect to baseline $\dot{V}O_2$, primary $\dot{V}O_2$ amplitude, or primary time delay. Minute ventilation, alveolar ventilation, and SpO₂ were assessed at isotime during the constant work rate exercise test. The IMW+ patients

had greater minute ventilations throughout (Figure 3) and greater alveolar ventilations at peak exercise. The IMW+ patients had greater exercise induced arterial desaturations at peak exercise compared to the IMW- patients (89.7 ± 3.2 vs 94.6 ± 2.7 %, $p = 0.02$; Figure 3).

We used multiple regression analyses to explore the associations between 6-MWT distance, $\dot{V}O_2$ kinetics, $\dot{V}O_{2peak}$ and PI_{max} . Regression analyses revealed significant correlations between the 6-MWT and PI_{max} ($r^2 = 0.69$; $p < 0.001$), the 6-MWT and $\tau \dot{V}O_2$ ($r^2 = 0.37$; $p < 0.01$), and $\dot{V}O_{2peak}$ with PI_{max} ($r^2 = 0.59$; $p < 0.01$; Figure 4).

Discussion

Our data indicates that inspiratory muscle weakness in COPD is associated with low 6-MWT distances and slowed $\dot{V}O_2$ kinetics.

According to previous studies (Rochester and Braun 1985; Begin and Grassino 1991; Saey et al. 2014), respiratory muscle strength is affected in patients with COPD (Gosselink et al. 1996). In the present investigation, a 48% prevalence rate of $PI_{max} < 60$ cmH₂O was found among patients with severe or very severe COPD, which is compatible with inspiratory muscle weakness (Ottenheijm et al. 2007; Gosselink et al. 2011). Moreover, the average absolute value of PI_{max} found was in accordance with a previous meta-analysis (Lotters et al. 2002). Interestingly, the presence of inspiratory muscle weakness may be associated with impaired pulmonary function in COPD patients. However, this does not adequately reflect systemic manifestations that contribute to reduced exercise performance (Celli et al. 2004). We have shown that slower oxygen uptake kinetics are closely associated with hyperinflation of the lung(s) in COPD patients (Chiappa et al. 2008; Chiappa et al. 2009). Interestingly, strategies that

reduce lung hyperinflation may accelerate oxygen uptake kinetics, and improve exercise performance (Chiappa et al. 2009).

In the present study, we found a significant correlation between the 6-MWT and PI_{max} , suggesting that inspiratory muscle weakness is associated with decreased functional capacity. Recently, Singer et al found a modest, but statistically significant, association between the distance walked in the 6-MWT and respiratory muscle weakness, in patients with COPD (Singer et al. 2011). However, this study included all GOLD severity levels, which may have affected the results. In our study, we only included severe to very severe COPD, which may have resulted in stronger correlations because of the avoidance of a ceiling effect in the association between PI_{max} and the 6-MWT, observed in patients with mild to moderate COPD (Singer et al. 2011). Studies have demonstrated a strong correlation between FEV_1 and the 6-MWT, which is a predictor of exercise capacity (Ijiri et al. 2014), suggesting that patients with peripheral and respiratory muscle weakness have reduced exercise capacity (Singer et al. 2011). In the present study, this response was dependent upon inspiratory muscle strength ($r = 0.83$; $p < 0.05$). Reduced muscle strength can result in diaphragm fatigue in patients with COPD, leading to the increased recruitment of accessory muscles and reducing ventilatory efficiency, as well as increasing the blood flow requirement to respiratory muscles during exercise.

The redistribution of blood flow to the respiratory muscles may be linked to a limitation in O_2 delivery, via increased intrathoracic pressure during hyperinflation and/or redistribution of blood flow away from the exercising limbs (Chiappa et al. 2008; Chiappa et al. 2009), affecting the muscle oxygenation during exercise in patients with COPD (Berton et al. 2010). Thus, the finding that COPD patients with IMW also

have a low O_2 pulse is consistent with the notion that expiratory flow limitation contributes to hyperinflation during exercise, limiting the increase in stroke volume and, potentially, O_2 delivery (Pessoa et al. 2013).

In patients with COPD, there is an exacerbation of respiratory sensitivity, affecting both the central and peripheral stimulation of chemoreceptors (Chiappa et al 2014). This is due to an overload of inspiratory muscles, typical of patients with COPD that have greater elastic and resistive breathing work (Gosker et al. 2003). These modifications can reflexively induce sympathetic vasoconstriction, and reduce blood flow to skeletal muscles during exercise (Harms et al. 1998; St Croix et al. 2000), affecting $\dot{V}\text{O}_2$ kinetics. We have shown that patients with COPD have slower $\dot{V}\text{O}_2$ kinetics (Chiappa et al. 2008), which may be due to limitations in the convective and/or diffusive transport of O_2 to skeletal muscle mitochondria and intramyocyte metabolic machinery.

Interestingly, changes associated with IMW can, therefore, result in reduced blood flow and/or O_2 delivery to the locomotor muscles, which could limit $\dot{V}\text{O}_2$ kinetics during constant work rate exercise. Diaphragm fatigue in COPD is known to contribute to sympathetic vasoconstriction of the vessels supplying the legs and may potentially limit $\dot{V}\text{O}_2$ kinetics (Nery et al. 1982; Palange et al. 1995; Somfay et al. 2002; Richardson et al. 2004; Borghi-Silva et al. 2008; Chiappa et al. 2008; Neder 2008). Alternatively, COPD patients with IMW had the greatest functional impairments, and therefore, were likely to have the greatest peripheral deconditioning (Maltais et al. 2014). As intramuscular mitochondrial expression is the primary determinant of $\dot{V}\text{O}_2$ kinetics in muscle cells (Poole and Jones 2012; Wust et al. 2013), it is also possible that deconditioning of both the respiratory and locomotor muscles underlies the association between PImax and $\dot{V}\text{O}_2$ kinetics.

An important limitation to this study was our use of a single transition to determine $\dot{V}O_2$ kinetics, which may limit the resolution of small differences in kinetic response, especially $\dot{V}O_2$. However, the differences between the IMW+ and IMW- patients were large enough to be detected statistically, as suggested by the study of Puente-Maestu et al (Puente-Maestu et al. 2001). Additionally, we used a constant pedaling cadence to determine T_{lim} at an intensity of $80\% \Delta \dot{V}O_2$ peak-GET, which elicits a $\dot{V}O_2$ slow component and rapid intolerance, and thus $\dot{V}O_2$ kinetics at this intensity may differ from $\dot{V}O_2$ kinetics below GET. However, we have successfully used this methodology in a previous study (Chiappa et al. 2008).

Our findings indicate that inspiratory muscle weakness is associated with slow $\dot{V}O_2$ kinetics and exercise intolerance in patients with COPD. It is currently unclear whether enhancing respiratory muscle strength, for example through inspiratory muscle training (Charususin et al. 2013), would help reverse slowed $\dot{V}O_2$ kinetics in patients with reduced respiratory muscle strength. Nevertheless, inspiratory muscle training in COPD may result in significant increases in aerobic capacity and exercise tolerance, as well as reduced dyspnea and increased quality of life (Kern and Kaushal 2014).

Conclusion

This study demonstrated that inspiratory muscle weakness in COPD patients is associated with low functional capacity (low 6MWT) and slowed $\dot{V}O_2$ kinetics.

Conflicts of interest

The authors state explicitly that there are no conflicts of interest about this article.

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Table 1. Characteristics of patients with and without inspiratory muscle weakness

	IMW+ (n = 22)	IMW- (n = 23)
<i>Demographic/anthropometric</i>		
Age, years	55 ± 5	54 ± 4
BMI, kg/m ²	24.8 ± 6.6	25.7 ± 6.4
Sex (male/female)	6/6	6/7
Forearm circumference, cm	25.2 ± 3.1	25.7 ± 1.9
MVC, kgf	60.8 ± 12.6	69.8 ± 19.3*
Fat mass, %	28.0 ± 13.7	29.9 ± 14.2
Muscle, %	34.8 ± 6.3	33.4 ± 6.6
Waist circumference, cm	92 ± 17.3	87.8 ± 13.2
Hip circumference, cm	93.6 ± 8.8	101.7 ± 10.8
Waist to hip ratio	0.9 ± 0.1	0.8 ± 0.08
<i>Lung function</i>		
FEV ₁ , %predicted	33 ± 11	36 ± 18
FVC, %predicted	82 ± 10	80 ± 13
FVC/FEV ₁	41 ± 12	45 ± 10

TLC, % predicted	112 ± 5	115 ± 3
IC, % predicted	73 ± 15	75 ± 13

Respiratory muscle function

P _I max, cm H ₂ O (%predicted)	36 ± 9.5 (35 ± 10)	88 ± 12* (87 ± 13)*
P _E max, cm H ₂ O (%predicted)	52 ± 14 (51 ± 12)	97 ± 28* (98 ± 25)*
P _{th} max, cm H ₂ O	20 ± 6.5	82.5 ± 54*
P _{th} max/P _I max, %	55 ± 11	92 ± 54*
Resistance time, s	94 ± 84	559 ± 92*

Drugs

Short-acting bronchodilator, (%)	20 ± 8	25 ± 9
Long-acting bronchodilator, (%)	80 ± 19	77 ± 26

IMW+ = positive inspiratory muscle weakness; IMW- = negative inspiratory muscle weakness; BMI = body mass index; MVC = maximum voluntary contraction; FEV₁ = forced expiratory volume in 1 s; BD = bronchodilator; FVC = forced vital capacity; FVC/FEV₁ = ratio between forced expiratory volume and forced vital capacity; P_Imax = maximum inspiratory pressure; P_Emax = maximum expiratory pressure; P_{th}max = maximal inspiratory muscle sustained;

Table 2 – Characteristics of sub-maximum and maximum exercise capacity of patients with chronic obstructive pulmonary disease with and without inspiratory muscle weakness

	IMW+ (n = 22)	IMW- (n = 23)
<i>Submaximal exercise</i>		
6MWT, m	288 ± 150	774 ± 220*
Borg dyspnea score	3.7 ± 1.6	2.8 ± 1.9
6-MWT/Borg dyspnea	40 ± 27	86 ± 81*
<i>Incremental exercise</i>		
$\dot{V}O_2$, mL/min	1170 ± 210	1823 ± 360*
$\dot{V}O_{2\text{GET}}$, mL/min	670 ± 87	780 ± 120
$\dot{V}E$, L	119.9 ± 28.42	93.9 ± 31.8
$\dot{V}E/MVV$	0.8 ± 17	0.9 ± 22
HR _{peak} , bpm	170 ± 13.8	158.1 ± 17.5
$\dot{V}O_2/HR$, mL.kg/bpm	9.9 ± 1.6	14.2 ± 2.3*
Power, watts	83.7 ± 20.8	108.1 ± 16.8*
Exercise time, min	6.8 ± 2.9	9.1 ± 1.2*
<i>Constant exercise</i>		
$\dot{V}O_{2\text{Basal}}$, mL	545 ± 115	568 ± 139

$\dot{V}O_2$ Amplitude, mL	645 ± 128	604 ± 89
$\dot{V}O_{2\tau}$, S	88 ± 28.6	$61 \pm 17.8^*$
$\dot{V}O_{2TD}$	17.5 ± 6.5	13.3 ± 7.0
$\dot{V}O_{2MRT}$, S	106.8 ± 22.3	$75.1 \pm 12.5^*$

IMW+ = positive inspiratory muscle weakness; IMW - = negative inspiratory muscle weakness; 6MWT = six-minute walk test; $\dot{V}O_2$ = oxygen consumption; $\dot{V}E$ = minute ventilation; $\dot{V}E/MVV$ = breathing reserve; HR = heart rate; $\dot{V}O_2/HR$ = oxygen pulse; τ = time constant; MRT = mean response time. * $p < 0.05$, IMW+ vs. IMW -

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Figure Captions

Figure 1 Flowchart of chronic obstructive pulmonary disease patient pathway.

Figure 2 Pulmonary oxygen uptake ($\dot{V}O_2$) kinetics at onset of high-intensity exercise according to age and inspiratory muscle weakness: without weakness (-), top panel; with weakness (+), bottom panel. Note the slower kinetics [higher time constant (τ) of the primary component] in chronic obstructive pulmonary disease patients with and without inspiratory muscle weakness.

Figure 3 Mean ($\pm$ SD) $\dot{V}E$, $\dot{V}A$, and $SatO_2$, at 0, 25, 50, 75 and 100% of isotime during a constant exercise protocol in chronic obstructive pulmonary disease patients with (filled circles) and without (open circles) inspiratory muscle weakness. $p > 0.05$ for the mean area under the curve in the two groups for $\dot{V}E$, $\dot{V}A$, and $SatO_2$.

Figure 4 Correlation analysis between VO_2 peak, 6-minute walk test and t (s) with PI_{max} for the groups of patients with (open circle) and without (closed circle) inspiratory muscle weakness.

Flowchart of chronic obstructive pulmonary disease patient pathway.

163x149mm (300 x 300 DPI)

Pulmonary oxygen uptake (VO₂) kinetics at onset of high-intensity exercise according to age and inspiratory muscle weakness: without weakness (–), top panel; with weakness (+), bottom panel. Note the slower kinetics [higher time constant (τ) of the primary component] in chronic obstructive pulmonary disease patients with and without inspiratory muscle weakness.

180x238mm (300 x 300 DPI)

Mean ($\pm$ SD) $\dot{V}_E$, V_A , and SpO_2 , at 0, 25, 50, 75 and 100% of isotime during a constant exercise protocol in chronic obstructive pulmonary disease patients with (filled circles) and without (open circles) inspiratory muscle weakness. $p > 0.05$ for the mean area under the curve in the two groups for $\dot{V}_E$, V_A , and SpO_2 .

128x205mm (300 x 300 DPI)

Correlation analysis between VO₂ peak, 6-minute walk test and t (s) with PImax for the groups of patients with (open circle) and without (closed circle) inspiratory muscle weakness.

228x411mm (300 x 300 DPI)