International Journal of COPD

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ORIGINAL RESEARCH

Relationship between oxygen consumption kinetics and BODE Index in COPD patients

This article was published in the following Dove Press journal:
International Journal of COPD
16 October 2012
Number of times this article has been viewed

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Background and objective: Patients with chronic obstructive pulmonary disease (COPD) present with reduced exercise capacity due to impaired oxygen consumption (VO_2), caused primarily by pulmonary dysfunction and deleterious peripheral adaptations. Assuming that COPD patients present with slower VO_2 and heart rate (HR) on-kinetics, we hypothesized that this finding is related to disease severity as measured by the BODE Index. In this context, the present study intends to evaluate the relationship between VO_2 uptake on-kinetics during high-intensity exercise and the BODE Index in patients with COPD.

Methods: Twenty males with moderate-to-severe stable COPD and 13 healthy control subjects matched by age and sex were evaluated. COPD patients were screened by the BODE Index and then underwent an incremental cardiopulmonary exercise test and a constant speed treadmill session at 70% of maximal intensity for 6 minutes. The onset of the exercise (first 360 seconds) response for O_2 uptake and HR was modeled according to a monoexponential fit.

Results: Oxygen consumption and HR on-kinetics were slower in the COPD group compared with controls. Additionally, VO_2 on-kinetic parameters revealed a strong positive correlation ($r = 0.77$, $P < 0.05$) with BODE scores and a moderate negative correlation with walking distance ($r = -0.45$, $P < 0.05$).

Conclusion: Our data show that moderate-to-severe COPD is related to impaired oxygen delivery and utilization during the onset of intense exercise.

Keywords: COPD, VO_2 on-kinetics, heart rate, BODE Index

Introduction

Patients with chronic obstructive pulmonary disease (COPD) present with reduced exercise capacity due to a combination of factors including impaired cardiopulmonary responses,[1] leading to inadequate pulmonary oxygen (O_2) uptake and delivery to active skeletal muscle,[2,3] derangements in the intracellular biochemical reactions in relation to mitochondrial oxygen consumption (VO_2)[4,5] and/or mechanical abnormalities.

Following the onset of constant workload exercise, the O_2 uptake increase (ie, on-kinetics) in COPD patient, which can be characterized by the time required for VO_2 to achieve steady state in response to physical stress, is slowed when compared to apparently healthy matched controls. From a clinical context, O_2 uptake on-kinetics has been shown to have even better prognostic value than peak VO_2 in chronic disease populations.[6,7] Moreover, recent studies have shown that, like O_2 uptake on-kinetics, heart rate (HR) on-kinetics, are also slower in COPD patients.[1,8] Some investigators[1,8,9] have postulated that slower O_2 uptake and HR on-kinetics[10] may reflect the adjustment of both oxygen delivery

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http://dx.doi.org/10.2147/COPD.S35637

and muscle metabolism during physical exercise[11] as well as exercise performance/functional capacity in these patients.

Additionally, forced expiratory volume in 1 second (FEV_1), a measurement that quantifies the degree of airway obstruction, is often used to diagnose and quantify COPD severity.[12] Moreover, the rate of decline in FEV_1 is a good marker of disease progression and mortality, however, it does not adequately reflect systemic manifestations that contribute to reduced exercise performance in COPD.[13]

The BODE Index, comprising of body mass index, airflow obstruction, dyspnea, and exercise capacity, has shown to be superior to FEV_1 in predicting clinical outcomes in the COPD population.[13] This multivariate scoring system can provide useful prognostic information in COPD and reflects functional disability induced by systemic consequences of this disease.[13,14] Recently, it have been suggested that serum C-reactive protein, an important systemic inflammation marker, combined with the BODE Index, has a higher combined prognostic value for patients with COPD.[15] In this context, on-kinetic alterations have been shown to be useful parameters to objectively evaluate the systemic consequences related to inability to perform submaximal exercise in COPD patients.[1]

In this context, the present study intends to evaluate the relationship between the metabolic demand during the onset of exercise and the BODE Index in patients with COPD. Assuming that COPD patients present with slower O_2 uptake and HR on-kinetics, which is an important index of exercise performance, we hypothesize that the slower O_2 uptake on-kinetic response is related to the level of disease severity, as represented by the BODE Index.

Methods

Study population

The study population was comprised of 20 men that volunteered to participate in the study with clinical and functional diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease[16] criteria, presenting with a FEV_1/forced vital capacity (FVC) of <0.7 and a postbronchodilator $FEV_1 < 60\%$ predicted.

No subject in the COPD group had ever participated in a pulmonary rehabilitation program. Criteria for inclusion were: adherence to the individually prescribed treatment regimen and disease stability indicated by no change in medication dosage or exacerbation of symptoms for at least 1 month prior to study enrollment. All patients presented with dyspnea during daily activities (Medical Research Council [MRC] grades II–III).[17] Exclusion criteria were: malignancy, orthopedic or neurological conditions affecting the ability to exercise, peripheral arterial disease, clinically apparent heart failure, and/or any renal, hepatic, or inflammatory disease.

Thirteen healthy control subjects (control group [CG]), matched according to age and sex, were also included in this investigation. Our laboratory posted an announcement at the university inviting healthy subjects to enroll as control subjects for this study. Subjects in the CG were free of any history of arterial hypertension, serious cardiac disease, or associated lung disease, were nonsmokers, and had not participated in regular daily physical activity during the past year. All participants signed a written informed consent and the study design was approved by the Human Ethics Committee of the Universidade Federal de Sao Carlos, Brazil, in compliance with the Declaration of Helsinki.

Measurements

Lung function

All patients underwent spirometry to quantify FEV_1 and FVC according to American Thoracic Society recommendations.[16] The values obtained were compared to the predicted normal values of Knudson et al.[18] Spirometry was performed using a Vitalograph® Hand-Held 2120 instrument (Ennis, Ireland), which was calibrated before each test according to manufacturer recommendations using a 1-L syringe.

Six-minute walking test (6MWT)

Performed as described by American Thoracic Society Guidelines.[19] Two tests were performed on alternating days within 48 hours. The test with the greatest six-minute walking distance (6MWD) was considered for analysis, as the first test tends to underestimate exercise capacity due to the subject's lack of familiarity with the test.[19] Each patient was instructed to walk from one end to the other, covering as much ground as possible during the allotted time and all patients were given standardized encouragement during the test.

BODE Index

Measurements to calculate this index were performed in all subjects in the COPD group. The BODE Index (B: body mass index; O: degree of airflow obstruction; D: dyspnea; E: exercise capacity), is a multidimensional index comprising of BMI, degree of airway obstruction (FEV_1), functional dyspnea (MRC dyspnea scale), and exercise capacity via the 6MWT. For calculation of the BODE Index, we used an empirical model as previously described.[13] For the first parameter, the value was 0 or 1. For the last three parameters, FEV_1, distance walked in 6 minutes, and score on the modified MRC dyspnea scale, the patients received points ranging from 0 (lowest value) to 3 (maximal value). The points for each variable were added, so that the BODE Index was the sum of points for each variable, ranging from 0 to 10 in each subject. The BODE Index can be divided into four quartiles: quartile I is a score of 0–2; quartile II is a score of 3–4; quartile III a score of 5–6; and quartile IV a score of 7–10.

Cardiopulmonary exercise testing (CPX)

Incremental symptom-limited exercise testing was performed on a treadmill using a computer-based ventilatory expired gas analysis system (VO_{2000}; Medgraphics Corp, St Paul, MN) in accordance with a previously described protocol.[20] The VO_{2000} uses a galvanic fuel cell for the oxygen analyzer (range 0%–96%) and a nondispersive infrared carbon dioxide analyzer (range 0%–10%), both of which were calibrated prior to each exercise test as per manufacturer instructions. A low-flow pneumotach (preVent Pneumotach, MGC; range 2–30 $L \cdot min^{-1}$) was calibrated with a 3-L volume syringe. Acceptable interday reliability for ventilation (CV 7.3%–8.8%), oxygen consumption (VO_2) and carbon dioxide (VCO_2; CV 5.3%–6.0%) has been demonstrated in a previous study.[21] VO_2 (in $mL \cdot min^{-1}$) was sampled for each three breaths and 10-second averaged data were recorded for further analysis. Oxyhemoglobin saturation (SpO_2, %) was determined by pulse oximetry (8500A; Nonin, Plymouth, MN). Subjects were also asked to rate their "shortness of breath" at exercise cessation using the 0–10 Borg's category-ratio scale.[22]

Constant speed exercise test (CSET)

The CSET were performed at 70% of the previously determined speed (during CPX) at 3° inclination on a treadmill, for 6 minutes. During the CSET, VO_2, SpO_2, HR, and the electrocardiogram were continuously monitored. The VO_2 and HR data from the onset of CSET were used for on-kinetics analysis.

On-kinetics analysis

In order to understand the behavior of HR and VO_2 during the onset of exercise, an on-kinetics analysis was performed for each variable.[23] The CSET VO_2 and HR data obtained were entered and analyzed into SigmaPlot 10.0, Systat Software (San Jose, CA) to be analyzed. In order to eliminate an occasional errant data point arising from coughs, sighs or swallows, VO_2 data that surpassed four standard deviations from the local mean was omitted.[24,25] The onset of exercise (first 360 seconds) response was modeled using a monoexponential fit.

$$f(t) = a_0 + a\,(1 - e^{-(t\text{-}TD)/\tau})$$

where 'f(t)' represents VO_2 or HR at any time (t); 'a_0' is the baseline value corresponding to a mean value at the last minute of baseline prior to the constant workload test; 'a' is the amplitude, ie, steady-state increase above baseline; 'τ' is the time constant, ie, the time taken to reach 63% of the function; and 'TD' is the time delay of the function. A warm-up was performed to minimize the effects of the cardiodynamic phase on the O_2 uptake on-kinetics response.[26] Additionally, the mean response time (MRT, the time taken to reach 63% of total response following the onset of exercise) was calculated as the weighted sum of the 'TD' and 'τ'.[27] The inclusion of 'TD' in this equation was established due the possibility that VO_2 or HR does not start to rise immediately at the onset of the imposed workload.[28] Given the fact that 'τ' and MRT are time parameters from an exponential function, the lower its values, the faster the VO_2 and/or HR response.[29,30]

To determine the parameters of the best curve fit, a nonlinear algorithm of least squares was used. This model adopts the minimization of the sum of square errors as a criterion for convergence. The 'a' and 'a_0' describe the parameters related to the component of Y axis (VO_2 or HR), the 'τ' and 'TD' describe the parameters related to X axis (time). Only the function with $r > 95\%$ was included in final analysis, which guarantees a good quality of fit.[28]

Statistical analysis

Sample size was based on the analysis of the 'τVO_2' values obtained in a pilot study (5 subjects) with $\beta = 0.8$ and $\alpha = 0.05$ (MedCalc Software, version 11.2.1.0 (Mariakerke, Belgium)). The results suggested at least 10 subjects in each group with differences of 5 seconds were needed to be sufficiently powered. The Shapiro–Wilk test was used to verify data distribution and heterogeneous variance (Levene test). Unpaired *t*-tests were used in the current analysis given all parameters demonstrated a normal distribution. The data were presented as mean and standard deviation. We used Pearson correlation analysis to evaluate the relationship between the variables. The level of significance was set at 5% (SigmaPlot version 11.0).

Results

Anthropometric characteristics

Table 1 lists the demographic characteristics of the subjects studied. There were no differences in age or anthropometric characteristics. Two patients had GOLD stage II COPD, ten had GOLD stage III and eight had stage IV of COPD. As expected, COPD subjects had lower values of pulmonary

Table 1 Age, anthropometric, and functional characteristics of COPD and control (CG) groups

	COPD (n = 20)	CG (n = 13)	*P* value
Age (years)	67.1 (±8.7)	64.8 (±8.9)	0.44
Anthropometric characteristics			
Body mass (kg)	62.6 (±12.9)	64.8 (±76)	0.31
Height (cm)	1.61 (±0.08)	1.63 (±0.08)	0.42
BMI (kg/m^2)	24.2 (±4.6)	25.3 (±3.46)	0.24
Pulmonary function			
VO_{2peak} (mL · min/kg)	15.05 (±3.32)	21.92 (±8.17)	0.002
FEV_1 (L)	0.8 (±0.24)	2.54 (±0.6)*	<0.001
FEV_1 %	31.8 (±9.5)	104 (±16.8)*	<0.001
FVC %	66.7 (±17.2)	108.8 (±18.3)*	<0.001
FEV_1/FVC	0.42 (±0.08)	0.77 (±0.06)*	<0.001
6MWT			
Distance (m)	358.6 (±111)	552 (±91.3)*	<0.001
Distance (% predict)	70.4 (±22.3)	106.2 (±18.1)*	<0.001
VO_2 (% VO_{2peak})	72.46 (±32.93)	70.52 (±27.58)	0.55
Function capacity			
MRC-0	4	–	
MRC-1	4	–	
MRC-2	3	–	
MRC-3	1	–	
MRC-4	8	–	
Mean BODE score	5.6 (±1.9)	–	
Quartile 1/2/3/4	1/4/10/5	–	

Notes: Data expressed as mean (±standard deviation); **P* < 0.05 Unpaired *t*-test.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MRC, Medical Research Council; 6MWT, Six-Minute Walking Test.

function compared with healthy controls. All subjects completed the 6MWT protocol without complication.

Table 2 lists values of O_2 uptake on-kinetics analysis achieved during the CSET. The COPD group exercise at a lower power output and achieved a lower VO_2 and HR "steady state" ('a', amplitude). Moreover, the time constant 'τ' associated with reaching VO_2 steady state was longer in COPD. The VO_2 and HR MRT was longer in the COPD group in compared with the CG ($P < 0.05$).

The Pearson correlation presented with a modest relationship between 6MWT distance and τVO_2 (Figure 1B; $r = -0.45$, $P < 0.05$) as well as FEV_1 ($r = -0.49$, $P = 0.05$). Interestingly, however, the relationship between the BODE Index and τVO_2 demonstrated a strong correlation (Figure 1A; $r = 0.77$, $P < 0.01$).

Finally, Figure 2 illustrates the mean fit of O_2 uptake and HR on-kinetics during CSET performed on a treadmill, which shows significant differences between the COPD and CG ($P < 0.05$). For the construction of these functions, the values obtained for the O_2 uptake on-kinetics analysis (the same listed in Table 2) were inserted in the kinetics equation described above and plotted as a function.

Discussion

The main important finding of the present study is that τVO_2 demonstrated a strong correlation with the BODE Index. In addition, this study revealed that O_2 uptake and HR on-kinetics were slower in the COPD group compared to the CG during CSET. These results indicate that a combined analysis of exercise on-kinetic responses and the BODE Index may serve as an important marker of diminished functional capacity, potentially indicating a worse prognosis in this patient population.

On-kinetics of oxygen uptake and heart rate

Due the fact that parameters "τ" and "MRT" are exponential time constants,[29] lower values indicate a better adjustment to exercise and more favorable physiologic function.

Based on the kinetic responses observed in the current study, we found that O_2 uptake and HR on-kinetics were slower (higher values of 'τ' and 'MRT') in COPD patients compared to the CG during CSET on a treadmill. In accordance with our results, several investigators[1,31,32] have reported that O_2 uptake on-kinetics are delayed in patients with COPD during constant work rate exercise on a cycle ergometer. The exact mechanism of slowed on-kinetics in patients with COPD is unclear, but Chiappa et al[1] demonstrated that it may be related to a prolonged O_2 delivery and

Table 2 On-kinetics parameters obtained during constant workload exercise tests (CWET) in COPD and control groups

	VO_2 kinetics			HR kinetics		
	COPD (n = 20)	Control (n = 13)	*P* value	COPD (n = 14)	Control (n = 11)	*P* value
Baseline	0.256 ± 0.1	0.3 ± 0.3	0.378	84.9 ± 7.1	80.6 ± 9.4	0.205
Amplitude	0.37 ± 0.2	0.7 ± 0.3*	0.001	29.3 ± 17.1	46.0 ± 13.0*	0.015
MRT (s)	73.9 ± 23.1	50.9 ± 10.4*	0.002	129.3 ± 52.1	111.7 ± 40.7	0.367
τ (s)	61.8 ± 25.5	40.5 ± 12.6*	0.009	126.2 ± 51.8	85.9 ± 35.9*	0.039

Notes: Data expressed as mean (±standard deviation). Amplitude and baseline are L/min and bpm for VO_2 and HR, respectively. Unpaired *t*-test: *statistically significant difference ($P < 0.05$) between COPD and control.
Abbreviations: HR, heart rate; COPD, chronic obstructive pulmonary disease; MRT, mean response time; *P*, statistical significance; τ, time constant.

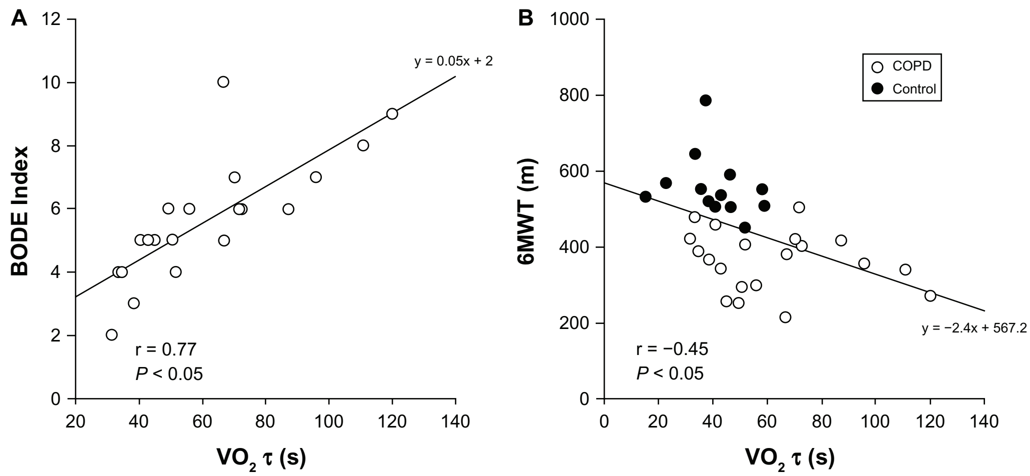

Figure 1 Relationship between the BODE Index (**A**) and the 6MWT (**B**) with the time constant (τ) for the on-transient of pulmonary oxygen (O_2) uptake in COPD patients.
Abbreviations: COPD, chronic obstructive pulmonary disease; 6MWT, 6-Minute Walking Test; $VO_2\tau$, oxygen uptake on kinetic.

utilization at the onset of exercise.[6] It is widely recognized that disturbances in the diffusive and/or convective transport of O_2 to skeletal muscle mitochondria[33,34] and/or intramyocyte metabolic machinery[35–37] could explain the attenuation of O_2 uptake on-kinetics in patients with cardiopulmonary and metabolic disorders.

In fact, hypoxemia,[3] autonomic imbalance,[38] blood flow redistribution from peripheral to respiratory muscles,[39,40] derangements in muscle vasodilatation capacity,[41] and increased intrathoracic and/or pleural pressures (swings on central hemodynamic adjustments) can all negatively impact the O_2 uptake response at the onset of exercise. Some therapeutic strategies[31,32,40,42] have been demonstrated to increase the O_2 uptake on-kinetics speed, supporting the importance of different interventions on the respiratory-mechanical system in order to improve functional capacity in COPD patients.

The other important issue investigated in the current study is slower HR on-kinetics identified in the experimental

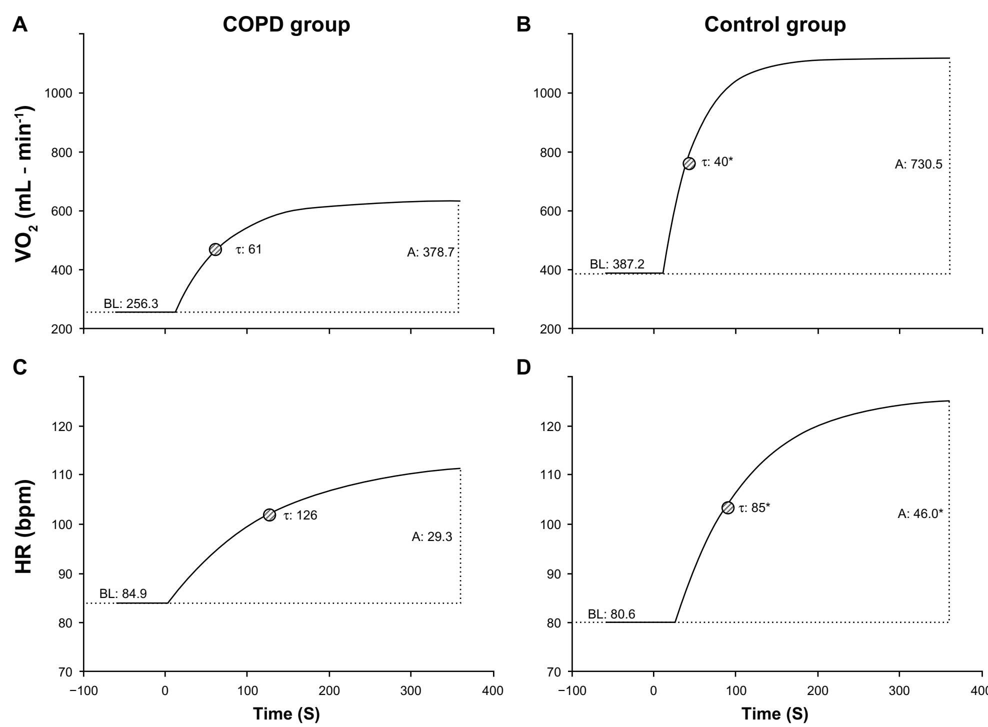

Figure 2 Illustration of the fitted curves using the means of VO_2 (**A** and **B**) and HR (**C** and **D**) kinetics during the constant-speed exercise tests (CSET) performed on a treadmill at intense exercise (70% of peak) in COPD (**A** and **C**) and control patients (**B** and **D**).
Abbreviations: COPD, chronic obstructive pulmonary disease; HR, heart rate; VO_2, oxygen consumption.

group, which has been previously described in patients with COPD.[1] In fact, cardiovascular responses that should help maintain adequate O_2 delivery to contracting muscle are impaired in COPD. Supposedly, slower HR on-kinetics can be explained by autonomic imbalance,[43] pulmonary vascular alteration, and/or effects of mechanisms of breathing on venous return.[38] Therefore, the assessment of HR on-kinetics may have particular clinical utility in reflecting physiologic function, disease severity and the response to therapeutic interventions in this chronic disease population.

On-kinetics: BODE Index relationship

The BODE Index has proven useful in evaluating the severity of COPD. As this index incorporates measures of airway obstruction, body mass composition, symptomatology and functional capacity, it captures a comprehensive panel of limitations induced by COPD. Assuming that severe COPD induces expressive peripheral muscle dysfunction and functional limitation, it seems rational to suspect that these patients presented with slowed O_2 uptake on-kinetics as an additional reflection of their advanced disease severity. Interestingly, however, in this regard the BODE Index demonstrated a strong correlation with O_2 uptake on-kinetics. In fact, the correlation was much stronger than for the 6MWD or FEV_1. These results may be explained by the fact that COPD has a systemic component that includes significant extrapulmonary effects that may contribute to disease severity variability amongst patients. In parallel, O_2 uptake and HR on-kinetics may infer the impairment of central cardiorespiratory and/or peripheral muscle in these patients.

To the best of our knowledge, this study is the first to assess the relationship between the BODE Index and O_2 uptake on-kinetics, which adds another dimension to BODE Index interpretation. Previous studies have shown that the BODE Index is correlated to other markers of functional performance. Regueiro et al[44] evaluated 10 moderate to severe COPD patients and demonstrated a strong correlation between the sit-to-stand test, hand grip strength test and the 6MWT (−0.86 against −0.45 in our study) and the BODE Index. These authors suggested that the BODE Index could be used to predict functional capacity. Simon et al[45] demonstrated that 39 patients with moderate to severe COPD presented a significant relationship between the BODE Index and physical activity assessed by the London Chest Activity of Daily Living Scale score. These authors suggested that BODE Index can therefore assist in the interpretability of the London questionnaire. Another recent study[46] was able to demonstrate that higher amounts of daily physical activity in 107 patients with moderate-to-severe COPD was associated with a lower BODE Index. In agreement, Mantoani et al[47] found a significant moderate correlation between the BODE Index and amount of daily physical activity in 67 patients with COPD. Accordingly, the results of the current study add to this body of literature by demonstrating a correlation between the BODE Index and another marker of exertional physiology, O_2 uptake on-kinetics. Thus, this allows us to infer that the BODE Index may reflect the degree of central/peripheral physiologic dysfunction induced by COPD and manifested by slower O_2 uptake and HR on-kinetics.

Limitations of this study

Firstly, it should be recognized that breath-by-breath analysis is the best way to obtain samples to fit the O_2 uptake on-kinetic response, however, other authors[48,49] have used this approach previously and showed reliability of the data collected[50] with good fit results. Secondly, the protocol used in this study was conducted on a treadmill. In fact, protocols on a cycle ergometer allow for a more precise measurement of external work rate. However, in this study we aimed to assess the functional capacity of COPD patients using an exercise mode that may more closely mimic activities of daily living (ie, ambulation). Moreover, exercise tests on a treadmill have been used to assess the on-kinetic response in the past.[25,51,52] Thirdly, we analyzed the time ('τ') to achieve 63% of steady rate, which may be overestimated by τHR if compared to other studies that used $T_{1/2}$ (50% of steady state).[1] However, we observed that the current study found COPD subjects presented with slower HR on-kinetics when compared to the CG, indicating a central limitation in these patients. Finally, we used a 6-minute protocol to analyze HR on-kinetics in order to compare it with O_2 uptake on-kinetic response. However, our results showed that the exponential model used to analyze the HR response may not be best represented by a 6-minute sample.

Importance of this study

Previous investigators have reported that COPD patients present with delayed O_2 uptake on-kinetics, which was also demonstrated in the current study using a constant speed on a treadmill. However, no previous investigation demonstrated that the degree of COPD severity is related to the O_2 uptake on-kinetic response. This is an important consideration as it adds another dimension to interpretation of the BODE Index, which is frequently employed in clinical practice. Delayed O_2 uptake and HR on-kinetics may be related to the reduction in exercise tolerance associated with poor prognosis assessed by the BODE Index in COPD patients.

Some therapeutic strategies that optimize exercise tolerance (ie, dynamic and/or strength training), accelerating exercise on-kinetics, may decrease the risk of exacerbations and death in these patients.[53] Additionally, O_2 uptake on-kinetics analysis can be used as a follow-up measure in many different therapeutic interventions.

Conclusion

In general, our data show that patients with moderate to severe COPD have impaired O_2 uptake and HR on-kinetics at the onset of intense exercise on a treadmill. In addition, we found a strong relationship between the BODE Index and O_2 uptake on-kinetics. Thus, COPD severity leads to an attenuated on-kinetics response during exercise which can be captured by the BODE Index.

Acknowledgments

This study received financial support from FAPESP (2009/01842-0) and CNPq (#483945/2007-2). The coauthors Thomas Beltrame (#130549/2011-8) and Michel Silva Reis received CNPq and PNPD-Capes fellowship, respectively. A Borghi-Silva is an Established Investigator (level II) of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil.

Disclosure

The authors report no conflicts of interest in this work.

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