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

Additionally, forced expiratory volume in 1 second (FEV₁), a measurement that quantifies the degree of airway obstruction, is often used to diagnose and quantify COPD severity. Moreover, the rate of decline in FEV₁ 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.

The BODE Index, comprising of body mass index, airflow obstruction, dyspnea, and exercise capacity, has shown to be superior to FEV₁ in predicting clinical outcomes in the COPD population. This multivariate scoring system can provide useful prognostic information in COPD and reflects functional disability induced by systemic consequences of this disease. Recently, it has 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. 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.

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 O₂ uptake and HR on-kinetics, which is an important index of exercise performance, we hypothesize that the slower O₂ 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 criteria, presenting with a FEV₁/forced vital capacity (FVC) of <0.7 and a postbronchodilator FEV₁ < 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). 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 FEV₁ and FVC according to American Thoracic Society recommendations. The values obtained were compared to the predicted normal values of Knudson et al. 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. 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. 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 (FEV₁), 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. For the first parameter, the value was 0 or 1. For the last three parameters, FEV₁, 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 (VO2max; Medgraphics Corp, St Paul, MN) in accordance with a previously described protocol. The VO2max 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⋅min⁻¹) was calibrated with a 3-L volume syringe. Acceptable interday reliability for ventilation (CV 7.3%–8.8%), oxygen consumption (VO2) and carbon dioxide (VCO2; CV 5.3%–6.0%) has been demonstrated in a previous study. VO2 (in mL⋅min⁻¹) was sampled for each three breaths and 10-second averaged data were recorded for further analysis. Oxyhemoglobin saturation (SpO2, %) 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.

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, VO2, SpO2, HR, and the electrocardiogram were continuously monitored. The VO2 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 VO2 during the onset of exercise, an on-kinetics analysis was performed for each variable. The CSET VO2 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, VO2 data that surpassed four standard deviations from the local mean was omitted. The onset of exercise (first 360 seconds) response was modeled using a monoexponential fit.

\[
f(t) = a_0 + a (1 - e^{(-t/\tau)})
\]

where ‘f(t)’ represents VO2 or HR at any time (t); ‘a0’ 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 O2 uptake on-kinetics response. 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’. The inclusion of ‘TD’ in this equation was established due the possibility that VO2 or HR does not start to rise immediately at the onset of the imposed workload. Given the fact that ‘τ’ and MRT are time parameters from an exponential function, the lower its values, the faster the VO2 and/or HR response.

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 ‘a0’ describe the parameters related to the component of Y axis (VO2 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.

Statistical analysis
Sample size was based on the analysis of the ‘τVO2’ values obtained in a pilot study (5 subjects) with β = 0.8 and α = 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
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 $V_O_2$ and HR “steady state” (“$a'$”, amplitude). Moreover, the time constant “$\tau$” associated with reaching $V_O_2$ steady state was longer in COPD. The $V_O_2$ and HR MRT was longer 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.

### Discussion

The main important finding of the present study is that $\tau V_O_2$ 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 “$\tau$” 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 “$\tau$” and ‘MRT”) in COPD patients compared to the CG during CSET on a treadmill. In accordance with our results, several investigators$^{1,3,1,3,2}$ 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 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 charac|              |             |         |
| Body mass (kg)        | 62.6 ± 12.9  | 64.8 ± 7.6  | 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    |              |             |         |
| $V_O_2$ ($\text{mL min/kg}$) | 15.05 ± 3.32 | 21.92 ± 8.17 | 0.002  |
| $FEV_1$ ($\text{L}$)  | 0.8 ± 0.24   | 2.54 ± 0.64 | <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  |
| $V_O_2$ (% $V_O_2$peak) | 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); $^a$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.

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

| $V_O_2$ kinetics | COPD (n = 20) | Control (n = 13) | P value |
|------------------|--------------|------------------|---------|
| Baseline         | 0.256 ± 0.1  | 0.3 ± 0.3        | 0.378   |
| Amplitude        | 0.37 ± 0.2   | 0.7 ± 0.3$^a$   | 0.001   |
| MRT (s)          | 73.9 ± 23.1  | 50.9 ± 10.4$^a$ | 0.002   |
| $\tau$ (s)       | 61.8 ± 25.5  | 40.5 ± 12.6$^a$ | 0.009   |

| HR kinetics      | COPD (n = 14) | Control (n = 11) | P value |
|------------------|--------------|------------------|---------|
| Baseline         | 84.9 ± 7.1   | 80.6 ± 9.4       | 0.205   |
| Amplitude        | 29.3 ± 17.1  | 46.0 ± 13.0$^a$ | 0.015   |
| MRT (s)          | 129.3 ± 52.1 | 111.7 ± 40.7     | 0.367   |
| $\tau$ (s)       | 126.2 ± 51.8 | 85.9 ± 35.9$^a$  | 0.039   |

Notes: Data expressed as mean (standard deviation). Amplitude and baseline are L/min and bpm for $V_O_2$ and HR, respectively. Unpaired t-test: $^a$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; $\tau$, time constant.
utilization at the onset of exercise. It is widely recognized that disturbances in the diffusive and/or convective transport of O₂ to skeletal muscle mitochondria and/or intramyocyte metabolic machinery could explain the attenuation of O₂ uptake on-kinetics in patients with cardiopulmonary and metabolic disorders.

In fact, hypoxemia, autonomic imbalance, blood flow redistribution from peripheral to respiratory muscles, derangements in muscle vasodilatation capacity, and increased intrathoracic and/or pleural pressures (swings on central hemodynamic adjustments) can all negatively impact the O₂ uptake response at the onset of exercise. Some therapeutic strategies have been demonstrated to increase the O₂ 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
group, which has been previously described in patients with COPD. 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, pulmonary vascular alteration, and/or effects of mechanisms of breathing on venous return. 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 expressory 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.\textsuperscript{33} 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.

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**Disclosure**

The authors report no conflicts of interest in this work.

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