Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics

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Submitted 21 December 2007; accepted in final form 13 March 2008

Chiappa GR, Borghi-Silva A, Ferreira LF, Carrascosa C, Oliveira CC, Maia J, Gimenes AC, Queiroga F Jr, Berton D, Ferreira EM, Nery LE, Neder JA. Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics. J Appl Physiol 104: 1341–1350, 2008. First published March 20, 2008; doi:10.1152/japplphysiol.01364.2007.—Patients with chronic obstructive pulmonary disease (COPD) have impaired exercise tolerance that characterizes this patient population (1, 3, 30, 33, 42, 44). Derangements in the diffusive and convective transport of O2 to skeletal muscle mitochondria (44, 45) and intramyocyte metabolic machinery (3, 54) could explain the slowness of V̇O2 kinetics in COPD. During moderate-intensity (sub-lactate threshold) exercise, the existing literature suggests that V̇O2 kinetics are limited by intramyocyte perturbations associated with COPD (34, 40, 45). However, a different scenario may emerge during heavy (supra-lactate threshold) exercise. In this situation, higher ventilation and disturbances in mechanics of breathing (1, 2, 49, 50), hypoxemia (36, 45), pulmonary hemodynamics (14), autonomic balance (26), and peripheral vasodilation (see discussion for details) could slow the response of systemic (central) and peripheral (microvascular) O2 delivery to a point where the kinetics of V̇O2 might become limited by O2 availability (38).

In this context, it can be anticipated that, if COPD slows the dynamic increase in muscle microvascular O2 delivery (QO2m) to a greater extent than the rate of O2 utilization, as indicated by the V̇O2 response following the onset of exercise, muscle microvascular O2 extraction would be accelerated (9, 16, 18). In this circumstance, the microvascular pressure of O2 might transiently reach levels sufficiently low to impair O2 transfer from capillary to mitochondria (38), predisposing the kinetics of V̇O2 to O2 delivery (convective and/or diffusive) limitation (39). In contrast, if the rate of increase in muscle microvascular O2 extraction is slowed in COPD patients at the onset of exercise, it would suggest that muscle O2 delivery is in excess of utilization throughout this transitional phase. These responses have been interpreted as V̇O2 kinetics being limited by activation of intracellular metabolic pathways (5, 10). This issue has been explored in healthy aging (9, 15, 16) and some chronic diseases [e.g., diabetes (6), peripheral arterial disease (5), and
heart failure (10)]. However, the effects of COPD on the dynamics of (estimated) muscle microvascular O2 extraction and central cardiovascular responses following the onset of heavy exercise remain unclear.

The main hypothesis tested in the present study is that the sluggish kinetics of VO2p commonly found in COPD patients are accompanied by faster adjustment of skeletal muscle deoxygenation (or estimated O2 extraction) and slower “central” cardiovascular dynamics [cardiac output (Qt)] following the onset of heavy-intensity exercise. Our secondary aims were to determine whether 1) an indicator of the dynamics of QO2m (approximately systemic O2 delivery); and 2) the ability of COPD patients to sustain exercise of heavy intensity is related to the kinetics of VO2p during the same exercise bout.

METHODS

Subjects

The study population comprised 10 men with clinical and functional diagnosis of COPD, according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria (33), and 11 age- and sex-matched sedentary controls. The patients were a subgroup of individuals referred from the outpatient clinic of our institution to participate on a larger clinical trial. Subjects were considered for study inclusion if the gas exchange threshold (GET) had been previously identified in a progressive exercise test (see below). Inclusion criteria for COPD patients were as follows: forced expiratory volume in 1 s (FEV1)-to-forced vital capacity ratio <0.7 and postbronchodilator FEV1 < 60% predicted; resting arterial Po2 > 60 Torr at room air; no evidence of severe pulmonary hypertension (estimated systolic pulmonary arterial pressure <40 mmHg) and preserved left ventricular function (ejection fraction >60%) by echo-Doppler cardiography; and clinical stability for at least 3 mo before the study and no use of oral corticosteroids in the preceding 6 mo. Subjects in the control group were free of chronic pulmonary, cardiovascular, immune, and metabolic disease. Before entering the study, all healthy controls were submitted to clinical evaluation, and they were screened by function tests, analysis of blood biochemistry, electrocardiography, echocardiography, and a stress exercise testing. To minimize the confounding effects of regular physical activity on the pathophysiology of exercise intolerance in COPD, we studied only patients and healthy controls who were sedentary during the year preceding admission to the study.

All participants signed a written, informed consent form. The study protocol was approved by the Medical Ethics Committee of the Federal University of São Paulo/São Paulo Hospital, Brazil.

Study Protocol

Subjects performed a ramp-incremental exercise test (5–10 W/min in patients and 15–20 W/min in controls) to determine parameters of aerobic function during exercise (52). The tests were performed on an electronically braked cycle ergometer (Corival 400, Lode) at 60 rpm, and they were preceded by an unloaded baseline pedaling at 0 W for 2 min.

The difference between VO2p at the GET (VO2p_GET) and VO2p at peak exercise (VO2p_peak) (∆VO2p_peak-GET) was determined from the ramp test. On a separate day, subjects performed a constant work rate exercise test at the same pedaling rate to the Tlim (min) at an intensity chosen to elicit a VO2p that exceeded the VO2p_GET by a value of ~40–50% of the ∆VO2p_peak-GET (~75% peak work rate). Tlim was defined as the time point in which the patients signaled to stop exercising or could not maintain the required pedaling rate for 10 s, despite being encouraged by the investigators.

Measurements

Pulmonary function tests. Spirometric tests were performed by using the CPF System (Medical Graphics-MGC, St. Paul, MN), with airflow being measured by a calibrated Pitot tube (PreVent Pneumotach). The subjects completed at least three acceptable maximal forced and slow expiratory maneuvers after the inhalation of 400 µg of salbutamol via metered-dose inhaler. Forced vital capacity (liters), FEV1 (liters), and inspiratory capacity (liters) were recorded. Carbon monoxide diffusing capacity was measured by the single-breath technique, and “static” lung volumes were obtained by body plethysmography. Arterial partial pressure for O2 and CO2 were determined in standard anerobic conditions (Torr).

Exercise tests. VO2p (ml/min), pulmonary carbon dioxide output (VCO2p; ml/min), minute ventilation (VE; l/min), and end-tidal partial pressures for O2 and CO2 (Torr) were measured breath by breath using a computer-based system (Cardio2 System, Medical Graphics). Gas exchange variables measured during the incremental test were averaged every 15 s, and VO2p_peak was defined as the highest value achieved during the test. Heart rate (HR; beats/min) was determined using the R-R interval from a 12-lead electrocardiogram. Arterial oxyhemoglobin saturation was determined by pulse oximetry [%SpO2], %; POX 010-340, Medaid, Torrance, CA] with its analog signal being directed to the system. Subjects were also asked to rate their “shortness of breath” at exercise cessation using the 0–10 Borg’s category ratio scale. The VO2p_GET was estimated by the gas-exchange method, inspecting visually the inflection point of VO2p with regard to VO2p (modified V-slope) (8) and by the ventilatory method when VE-to-VO2p ratio and end-tidal partial pressure of O2 increased, while VE-to-VCO2p ratio and end-tidal partial pressure of CO2 remained stable. The reading was performed independently by two experienced observers without knowledge of other results or subject identities.

Skeletal muscle oxygenation. Skeletal muscle oxygenation profiles of the left vastus lateralis were evaluated with a commercially available near-infrared spectroscopy (NIRS) system (Hamamatsu NIRE 200, Hamamatsu Photonics KK). The theory of NIRS has been described in detail elsewhere (17). Briefly, one fiber-optic bundle carried the near-infrared light produced by the laser diodes to the tissue of interest, while a second fiber-optic bundle returned the transmitted light from the tissue to a photon detector in the spectrometer. The intensity of incident and transmitted light were recorded continuously and, along with the relevant specific extinction coefficients, used to measure changes in the oxygenation status of hemoglobin + myoglobin (Hb + Mb). A set of optodes was placed on the belly of the vastus lateralis muscle midway between the lateral epicondyle and greater trochanter of the femur. The optodes were housed in an optically dense plastic holder, thus ensuring that the position of the optodes, relative to each other, was fixed and invariant. The optode assembly was secured on the skin surface with tape and then covered with an optically dense, black vinyl sheet, thus minimizing the intrusion of extraneous light and loss of near-infrared light.

The variables assessed by NIRS are the concentration of oxygenated, deoxygenated, and total Hb. Among the NIRS variables, several laboratories have adopted the deoxy-Hb/Mb signal (deoxy-Hb concentration [HHb]) as the preferred indicator of changes in muscle microvascular oxygenation during exercise (15, 16, 19, 24, 28). The [HHb] response to exercise is then considered a proxy of O2 extraction in the microcirculation, reflecting the balance between O2 delivery and utilization. The device used herein did not measure the reduced scattering of the tissue, preventing determination of absolute values of [HHb] (in µM). Therefore, the [HHb] values were recorded as a change (Δ) from baseline in units of micromoles per centimeter. The NIRS system was “zeroed” during the unloaded cycling portion of the tests.

Central hemodynamics. Qt (l/min) and stroke volume (SV; liters) were measured noninvasively throughout the constant work rate test using impedance cardiography (PhysioFlow PF-05, Manatec Biomed-
V̇O₂p, Q̇T, SV, and HR data from 30 s of baseline pedaling to 180 s of exercise. Our investigation is characterized by the presence of a slow component of V̇O₂p, Q̇T, and [HHb] (34). Therefore, the data relative to the first 20 s after exercise onset, i.e., the exponential response of interest. In the analysis of Q̇T, HR, and SV, SpO₂ values on [HHb] in the patient group, the following correction within this time window. To reduce the potential influence of low SpO₂ values on [HHb] was estimated as the change from 3 min to the end of exercise (end-3 min). The V̇O₂p responses to exercise in the intensity domain used in the study (see Methodological Considerations), we opted to fit V̇O₂p, Q̇T, SV, and HR data from 30 s of baseline pedaling to 180 s after the onset of exercise. Using this approach and Eq. 2 (see below), we ensured that the same amount of data was included in the kinetic analysis of V̇O₂p, and hemodynamics for each subject (controls and patients), minimizing model-dependent effects on our results. For [HHb] kinetics, the analyses were conducted on data from 30-s baseline cycling to the first 60 s following the increase in work rate to minimize distortion of the curve-fitting seen when longer periods are analyzed (15, 16, 18, 19). Theoretical (18) and empirical studies (15, 16, 24) suggest the primary phase of the HHb response is complete within this time window. To reduce the potential influence of low SpO₂ values on [HHb] in the patient group, the following correction (\([\text{HHb}_{\text{corr}}]\)) was applied:

\[
[\text{HHb}_{\text{corr}}] = [\text{HHb}] - \left(1 - \sqrt{\frac{1}{2/\text{SpO}_2}}\right)
\]

The model used for fitting the kinetic response of V̇O₂p, Q̇T, SV, HR, and [HHb] was

\[
\left[\text{Y}\right]_t = \left[\text{Y}\right]_0 + A \cdot \left[1 - e^{-t/\text{TD}_p}\right]
\]

where \([\text{Y}]\) is the variable under analysis the subscripts b and p are baseline unloaded cycling and primary component, respectively; and A is amplitude, TD is time delay, and \(t\) is time constant of the exponential response of interest. In the analysis of Q̇T, HR, and SV, the TDp was dropped from the equation. For V̇O₂p analysis, we deleted the data relative to the first 20 s after exercise onset, i.e., the cardio-dynamic phase (34). Therefore, \(t_\text{p}V̇O₂p\) represents the time course of the primary component of the response, an estimate of the muscle V̇O₂p kinetics (23, 53). The overall kinetics of [HHb] (approximate time to reach 63% of the response following the onset of exercise) were determined by the mean response time (MRT = \(\tau + \text{TD}\)). In addition, the amplitude of the “slow component” of V̇O₂p, Q̇T, and [HHb] was estimated as the change from 3 min to the end of exercise (end-3’). Statistical Analysis

The SPSS version 13.0 statistical software was used for data analysis (SPSS, Chicago, IL). Results were summarized as means ± SD, or median and ranges for symptom scores. To contrast between-subject resting and exercise responses, nonpaired t or Mann-Whitney tests were used, as appropriate. One-way ANOVA was used to contrast MRT values: a post hoc analysis was performed with Scheffé’s test when appropriate. Pearson’s product-moment correlation was 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 V̇O₂p, Q̇T, and [HHb] was significantly different from zero. The level of statistical significance was set at \(P < 0.05\) for all tests.

RESULTS

Subject Characteristics and Exercise Tolerance

Subjects’ resting characteristics are presented in Table 1. There were no between-group differences in age and body mass index. As expected from the inclusion criteria, patients had moderate-to-severe airflow obstruction with increased “static” lung volumes and moderate reductions in carbon monoxide diffusing capacity. Seven patients were classified as GOLD stage II, with the remaining patients being considered as GOLD stages III-IV (33).

V̇O₂p peak, peak work rate, and V̇O₂p GET were significantly reduced in patients compared with controls; in contrast, \(V_E\)-to-maximal voluntary ventilation ratio and dyspnea scores were higher in patients (Table 2). Six patients had exercise-related oxyhemoglobin desaturation, i.e., SpO₂ decrease ≥4% (lowest values at peak exercise ranging from 86 to 89%). The tolerance to high-intensity, constant work rate exercise (Tlim) was significantly reduced in patients compared with controls (640 ± 95 s vs. 371 ± 100 s; \(P < 0.001\)). In similarity with the maximal exercise test, \(V_E\)-to-maximal voluntary ventilation ratio and dyspnea were higher in patients, with six patients showing a significant decrease in SpO₂ (lowest values at exercise cessation ranging from 86 to 88%).

Pulmonary Gas Exchange and Cardiovascular Adjustments

Representative responses of V̇O₂p and Q̇T are shown in Figs. 1 and 2, respectively. The dynamics of V̇O₂p were slower in patients than controls (Table 3, Fig. 3). In sub-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>COPD</th>
</tr>
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<tbody>
<tr>
<td>(n)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Demographic/anthropometric</td>
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<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>61.4±6.3</td>
<td>59.8±7.9</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>24.3±3.0</td>
<td>25.1±2.2</td>
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<td>Pulmonary function</td>
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<td>FEV₁, liters</td>
<td>3.31±0.50</td>
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<tr>
<td>FEV₁, %predicted</td>
<td>99.6±9.4</td>
<td>44.0±15.8*</td>
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<tr>
<td>FVC, %predicted</td>
<td>103.2±10.1</td>
<td>84.0±12.3*</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>94.4±5.8</td>
<td>46.0±17.8*</td>
</tr>
<tr>
<td>TLC, %predicted</td>
<td>87.6±2.3</td>
<td>119.0±3.7*</td>
</tr>
<tr>
<td>RV, %predicted</td>
<td>103.9±5.44</td>
<td>165.0±52.8*</td>
</tr>
<tr>
<td>IC, %predicted</td>
<td>97.0±11.3</td>
<td>75.5±21.3*</td>
</tr>
<tr>
<td>DLCO, %predicted</td>
<td>86.7±9.8</td>
<td>47.5±12.5*</td>
</tr>
<tr>
<td>Pao₂, Torr</td>
<td>72±7</td>
<td>20±2</td>
</tr>
<tr>
<td>Paco₂, Torr</td>
<td>35±5</td>
<td>38±5</td>
</tr>
</tbody>
</table>

*Values are means ± SD; \(n\) no. of subjects. COPD, chronic obstructive pulmonary disease; \(FEV₁\), forced expiratory volume in 1 s; \(FVC\), forced vital capacity; TLC, total lung capacity; \(RV\), residual volume; \(IC\), inspiratory capacity; \(DLCO\), lung diffusing capacity for carbon monoxide; \(Pao₂\), and \(Paco₂\), arterial \(O₂\) and \(CO₂\), respectively; \(SaO₂\), arterial \(O₂\) saturation. *\(P < 0.05\).
In similarity with \( \dot{V}O_2p \), a slow component of \( \dot{Q}_T \) was found in 86.7 slower in patients compared with controls (HR: 61.4 COPD patients, we evaluated the kinetics of HR and SV faster than the \( \dot{V}O_2p \) and \( \dot{Q}_T \) responses in both groups (Table 3, the \([HHb]\) increased rapidly with response kinetics that were showed a transient decrease in \([HHb]\) early into the exercise, previously described, the \([HHb]\) response displayed a region in representative patient and a normal control are shown in Fig. 6. As

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls Incremental Exercise</th>
<th>COPD Incremental Exercise</th>
<th>Controls Constant Work Rate Exercise</th>
<th>COPD Constant Work Rate Exercise</th>
</tr>
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<td>( n )</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Power, W</td>
<td>13.0 ± 15</td>
<td>9.1 ± 2.4*</td>
<td>95 ± 17 W</td>
<td>70 ± 16*</td>
</tr>
<tr>
<td>( V_{O2} ), ml/min</td>
<td>1.595 ± 256</td>
<td>1.320 ± 194*</td>
<td>1.388 ± 197</td>
<td>1.158 ± 218*</td>
</tr>
<tr>
<td>( V_{CO2} ), ml/min</td>
<td>1.860 ± 343</td>
<td>1.427 ± 330*</td>
<td>1.490 ± 298</td>
<td>1.227 ± 303*</td>
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<tr>
<td>RER</td>
<td>1.19 ± 0.12</td>
<td>1.07 ± 0.14</td>
<td>1.10 ± 0.10</td>
<td>1.05 ± 0.08</td>
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<tr>
<td>( V_{O2} ) at the GET, ml/min</td>
<td>1.215 ± 202</td>
<td>1.008 ± 174*</td>
<td>53.8 ± 11.7</td>
<td>41.7 ± 10.8*</td>
</tr>
<tr>
<td>( V_{E} ), l/min</td>
<td>67.2 ± 13.9</td>
<td>43.8 ± 9.4*</td>
<td>0.30 ± 0.06</td>
<td>0.86 ± 0.09*</td>
</tr>
<tr>
<td>([HHb])/MVV</td>
<td>0.35 ± 0.08</td>
<td>0.88 ± 0.10*</td>
<td>78.4 ± 8.7</td>
<td>75.3 ± 10.1*</td>
</tr>
<tr>
<td>Heart rate, %predicted</td>
<td>88.9 ± 8.9</td>
<td>82.5 ± 9.6</td>
<td>94.4</td>
<td>92.2</td>
</tr>
<tr>
<td>( Sp_{O2} ) %</td>
<td>95.4</td>
<td>92.3</td>
<td>7 (3–9)*</td>
<td>7 (4–10)*</td>
</tr>
<tr>
<td>Dyspnea scores</td>
<td>4 (2–9)</td>
<td>7 (3–9)*</td>
<td>3 (1–7)</td>
<td>7 (4–10)*</td>
</tr>
<tr>
<td>Leg effort scores</td>
<td>5 (4–10)</td>
<td>7.5 (0–10)</td>
<td>5 (4–8)</td>
<td>7 (1–9)</td>
</tr>
</tbody>
</table>

Values are means ± SD with the exception of symptoms (median and range); \( n \), no. of subjects. \( V_{O2} \), oxygen uptake; \( V_{CO2} \), carbon dioxide output; RER, respiratory exchange rate; GET, gas exchange threshold; \( V_{E} \), minute ventilation; MVV, maximal voluntary ventilation; \( Sp_{O2} \), oxymoglobin saturation by pulse oximetry. *\( P < 0.05 \) (between-group differences in a given exercise testing protocol).

The increase in \( Q_T \) was slower in patients compared with controls and longer than those of \( V_{O2} \) in both groups (Table 3, Fig. 3). To gain further insights into the slowing of \( Q_T \) of COPD patients, we evaluated the kinetics of HR and SV (Fig. 5). The dynamics of both variables were significantly slower in patients compared with controls (HR: 61.4 ± 12.2 vs. 86.7 ± 13.9 s; SV: 42.3 ± 10.1 vs. 64.3 ± 11.0 s, \( P < 0.01 \)). In similarity with \( V_{O2} \), a slow component of \( Q_T \) was found in all subjects (\( P < 0.05 \)). There were no between-group differences in the magnitude of the \( V_{O2} \) slow component \( \Delta[\dot{V}_O2_{end-3}] = 202 ± 99 \) vs. 185 ± 89 ml/min for patients and controls, respectively, and the relationship between \( \Delta[\dot{V}_O2_{end-3}] \) and \( T_{lim} \) was not significant in either group (\( P > 0.05 \)).

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**Muscle Oxygenation Responses**

The dynamics of \( Sp_{O2} \) corrected \([HHb]\) values for a representative patient and a normal control are shown in Fig. 6. As previously described, the \([HHb]\) response displayed a region in which the signal remained stable or decreased transiently (determined here by the time delay) (e.g., Fig. 6). All subjects showed a transient decrease in \([HHb]\) early into the exercise, with similar duration in both groups (Table 3). After this phase, the \([HHb]\) increased rapidly with response kinetics that were faster than the \( V_{O2}p \) and \( Q_T \) responses in both groups (Table 3, Fig. 3). \( \tau[HHb] \) (Table 3) and MRT-[HHb] (Fig. 3) were significantly faster in patients compared with normal controls.

A slow-component of \([HHb]\) was observed in all subjects of the control group \( \Delta[HHb]_{(end-3)} \) (\( P < 0.05 \)). In contrast, only four patients displayed a slow component of the \([HHb]\) response. The \( \Delta[HHb]_{(end-3)} \) was significantly related to \( \Delta[\dot{V}_O2p]_{(end-3)} \) in the control group (\( r = 0.72, P < 0.01 \)), but not in patients (\( P = 0.38 \)).

**Dynamics of Estimated \( \dot{Q}_{O2m} \)**

We also calculated an indirect index of the dynamics of \( \dot{Q}_{O2m} \) (\( \dot{Q}_{O2m} \) ~ \( \dot{V}_{O2p}/MRT[HHb] \)) (see DISCUSSION for further elaboration). This ratio was significantly higher in patients compared with controls (4.9 ± 1.2 vs. 2.5 ± 0.6, respectively; \( P < 0.01 \)), suggesting that \( \dot{Q}_{O2m} \) adapted at a slower rate in patients. Interestingly, \( \dot{Q}_{O2m} \) was closely related to MRT-Qr (Fig. 7), suggesting that the dynamics of \( \dot{Q}_{O2m} \) followed the response characteristics of systemic ("central") \( O_2 \) delivery.

**DISCUSSION**

Several aspects make this study a novel investigation. Specifically, this is the first study to measure \( V_{O2p} \), \( Q_T \), and tissue oxygenation kinetics simultaneously following the onset of heavy-intensity leg cycling exercise in patients with moderate-to-severe COPD. This is the initial step to establish if key determinants of the dynamic matching of central and peripheral (microvascular) \( O_2 \) delivery-to-\( \dot{V}_O2 \) are impaired by COPD and set the stage for future interventional studies. We found that \( V_{O2p} \) kinetics were slower in COPD patients than in controls and correlated with the tolerance to sustain heavy-intensity exercise. In addition, compared with the age-matched controls, COPD patients displayed slower kinetics of \( Q_T \) and faster dynamics of \([HHb]\). Interpretation of the latter as an estimate of muscle microvascular \( O_2 \) extraction suggests that the dynamics of muscle \( \dot{Q}_{O2m} \) were slower in COPD patients. Accordingly, a qualitative index of \( \dot{Q}_{O2m} \) kinetics (ratio of \( \dot{V}_{O2p} \) to MRT-[HHb]) was greater in COPD patients and was closely related to the overall kinetics of \( Q_T \). These data, therefore, indicate that impaired central and peripheral cardiocirculatory adjustments following the onset of heavy-intensity exercise negatively impact the dynamic matching of \( O_2 \) delivery and utilization in patients with COPD.

*J Appl Physiol* • VOL 104 • MAY 2008 • www.jap.org
Several groups have reported that VO₂ kinetics are slowed by healthy aging (9, 11, 15, 16), and this could be due to impairments in the dynamics of O₂ delivery (15, 16). In general, data from our control group describing the kinetics of VO₂ and central cardiovascular responses to heavy exercise are in close agreement with previous studies (9, 11, 15, 16). In COPD patients, the kinetics of VO₂ during moderate-intensity (sublactate threshold) exercise are 45–65% slower than in healthy aged controls (34, 36, 40). We extended these findings to show that VO₂ kinetics during heavy-intensity exercise were, on average, 74% slower in COPD patients (Table 3). Moreover, phase II VO₂ kinetics displayed an inverse relationship with tolerance to sustain heavy-intensity exercise (Fig. 4). These data are consistent with those from the study of Puente-Maestu and coworkers (40), who found a significant inverse correlation between increase in Tlim during moderate exercise and the decrease in τVO₂ induced by exercise training in patients with advanced COPD. Our data and those of Puente-Maestu et al. (40) collectively suggest that abnormalities on muscle energetics following the onset of exercise may contribute to the patient’s ability to sustain dynamic exercise for prolonged periods of time. Thus resolution of factors that promote the slowing of VO₂ response in COPD might prove to be useful in guiding therapeutic efforts to increase the tolerance to heavy-intensity exercise in this population.

Potential Mechanisms for a Slower VO₂ Kinetics at Heavy-intensity Exercise in COPD

The factors generally considered as limiting the kinetics of VO₂ are the adequacy of O₂ delivery during the transient phase following the onset of exercise (27) and/or the activity of intracellular biochemical reactions that stimulate mitochondrial VO₂, also called “metabolic inertia” (23). Several groups emphasize the role of O₂ delivery limitation to VO₂ kinetics in the elderly (9, 15, 16) and in chronic diseases (5, 6, 10). The argument for O₂ delivery limitation of VO₂ kinetics in old subjects is based on slower adaptation of HR (16) and age-related changes in arteriolar vasodilation (7). More recently, these arguments have been strengthened by faster kinetics of muscle deoxygenation at the onset of heavy-intensity exercise in old compared with young individuals (9, 15, 16), suggesting that, in the former group, the dynamics of muscle perfusion were slower in relation to the kinetics of muscle VO₂ (18). Moreover, interventions that appear to increase muscle oxygenation promoted a speeding of VO₂ kinetics in the elderly (15). If derangements in O₂ delivery explain, at least partially, the slowing of VO₂ kinetics with healthy aging, it is conceivable that any pathological condition that could further slow the

\[ \tau = \text{time constant} \]

\[ \tau = 53 \, \text{s} \]

\[ \tau = 73 \, \text{s} \]

\[ \tau = 70 \, \text{s} \]

\[ \tau = 100 \, \text{s} \]

Fig. 1. Pulmonary O₂ uptake (VO₂p) kinetics (phases II and III) at the onset of heavy-intensity exercise in a representative age-matched control (A) and a patient with chronic obstructive pulmonary disease (COPD; B). Note the slower kinetics [higher time constant (τ) of the “primary” component] in the COPD patient compared with the control subject.

Fig. 2. Cardiac output (Qr) adjustment at the onset of heavy-intensity exercise in a representative age-matched control (A) and a patient with COPD (B). Note the slower “central” cardiovascular adaptation to exercise [higher mean response time (MRT) = τ + time delay (TD)] in the COPD patient compared with the control subject.
dynamics of convective O₂ delivery in old individuals (e.g., COPD) would have a negative impact on the kinetics of VO₂p during heavy-intensity exercise. However, to elucidate the main determinant of slower VO₂p kinetics, one must consider which of the potential limiting factors (intramyocyte metabolic machinery or O₂ delivery) is affected to a greater extent, if any, by the disease.

Patients with COPD have decreased oxidative enzyme activity and mitochondrial volume density and an increase in the percentage of type II fibers (as reviewed in Ref. 3). This intrinsic skeletal muscle dysfunction could, at least partially, explain the slowing of VO₂p kinetics in COPD patients. Consistent with this notion, VO₂p kinetics of COPD patients performing moderate exercise were not affected by hyperoxic gas breathing (45), which was assumed to increase muscle O₂ delivery. Moreover, exercise training speeded the kinetics of VO₂p with no effect on HR dynamics, which is usually considered an indicator of QT and O₂ delivery kinetics (12). Thus, in lieu of similar O₂ delivery following the onset of heavy-intensity exercise, intrinsic skeletal muscle dysfunction would solely explain the slower VO₂p kinetics observed in the present study (Figs. 1 and 3). Several variables measured and estimated in our study suggest this may not be the case during heavy-intensity exercise in patients with moderate-to-severe COPD.

Dynamics of QT During Dynamic Exercise in COPD

A slower adjustment of HR to moderate exercise in patients with COPD than in age-matched controls has been previously described (34, 40). Numerous factors (see below) can also impair the adjustment of SV following the onset of exercise in COPD, such that HR dynamics may underestimate the impact of the disease on the kinetics of QT. Our study is the first to show that QT (approximately O₂ delivery) kinetics were ~44% slower in COPD patients compared with healthy peers. This was a consequence of slower SV and HR kinetics, where, on average, the SV response appeared to be affected to a greater extent than HR (~52 vs. ~40% higher time constant). This demonstrates that central cardiovascular responses that help maintain the adequacy of O₂ delivery to contracting muscles are impaired in COPD. In the present study, these derangements are unlikely to be related to intrinsic cardiovascular disease, as the patients were clinically and functionally screened for significant inotropic dysfunction and severe pulmonary hypertension.

Potential explanations for slower on-transient QT (i.e., HR and SV) kinetics in COPD are as follows: 1) autonomic imbalance (26), 2) pulmonary vascular alterations (including pulmonary hypertension) (14), and/or 3) effects of mechanics of breathing on SV (1, 2, 49, 50). The increase in HR through sympathetic activation is slower than that accomplished by parasympathetic withdrawal (51). The shift toward greater sympathetic activity with COPD (26) would promote slowing of HR and thereby QT dynamics. Regarding the SV response, the deleterious cardio-circulatory consequences of increasing

<table>
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<tr>
<th>Parameters</th>
<th>Controls</th>
<th>VO₂p</th>
<th>COPD</th>
<th>Controls</th>
<th>QT</th>
<th>COPD</th>
<th>Controls</th>
<th>[HHb]</th>
<th>COPD</th>
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<tr>
<td>Baseline</td>
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<td>510±110</td>
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<tr>
<td>A</td>
<td>865±156</td>
<td>691±250</td>
<td>5.4±2.3</td>
<td>6.4±2.3</td>
<td>73.3±46.7</td>
<td>60.1±30.5</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>τ, s</td>
<td>42.1±12.9</td>
<td>72.9±23.3*</td>
<td>66.6±10.8</td>
<td>96.2±31.6*</td>
<td>9.8±1.4</td>
<td>6.7±1.2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TD, s</td>
<td>6.5±5.0</td>
<td>7.8±7.7</td>
<td>—</td>
<td>9.2±3.2</td>
<td>10.3±3.9</td>
<td></td>
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Values are means ± SD. VO₂p, pulmonary VO₂; QT, cardiac output; [HHb], deoxyhemoglobin concentration; A, amplitude; τ, time constant; TD, time delay. *P < 0.01.

Fig. 3. MRT (in s) (MRT = τ + TD) of VO₂p, QT, and deoxy-hemoglobin concentration ([HHb]) measured by near-infrared spectroscopy at the onset of heavy-intensity exercise in age-matched controls (open bars) and patients with COPD (solid bars). Note that the dynamics of VO₂p and QT were slower in patients with COPD; in contrast, they presented with faster [HHb] kinetics than the healthy controls. Values are means (SD). *P < 0.05 for between-group comparisons; †P < 0.05 for within-group comparisons of VO₂p vs. QT and [HHb]; ‡P < 0.05 for within-group comparisons of QT vs. [HHb].

Fig. 4. Significant inverse relationship between time to intolerance in response to heavy-intensity exercise and the τ of the “primary” component of the on-transient VO₂p kinetics in patients with COPD (●) but not in healthy controls (○).
lung volumes in patients with COPD, especially during exercise, have been emphasized (1). More specifically, the development of high mean intrathoracic pressures as \( V_\text{E} \) increases in the transitional phase could dynamically impair the rate of right ventricle filling and left ventricle emptying in these patients. Recently, Vogiatzis et al. (49) showed that normal subjects breathing with simulated expiratory flow limitation, similar to that found in advanced COPD, had significantly slower off-transient \( V_\text{O}_2p \) kinetics compared with control values, suggesting that alterations in the mechanics of breathing can reduce muscle \( O_2 \) delivery enough to affect the kinetics of \( V_\text{O}_2p \).

Another relevant mechanism for a reduced \( O_2 \) delivery to the working muscles could be related to the pattern of respiratory muscle recruitment in patients with advanced COPD. Aliverti and Macklem (1) postulated that slowing the velocity of shortening of the abdominal expiratory muscles, by increasing expiratory pressures, had major adverse effects on the circulation impeding venous return and decreasing \( Q_\text{T} \). Considering that some patients seem to recruit massively the abdominal muscles (2), it is conceivable that these adjustments could impair peripheral \( O_2 \) delivery. Moreover, respiratory muscle work during heavy exercise can divert a fraction of the \( Q_\text{T} \) from leg muscles, contributing to exercise intolerance (25). Since the work of breathing is particularly increased in COPD patients (1), following the onset of exercise, a larger portion of \( Q_\text{T} \) may be directed to the diaphragm, predisposing to slower kinetics of peripheral muscle blood flow in COPD compared with controls. These findings support the notion that central cardiovascular responses to exercise and peripheral \( O_2 \) delivery can be

![Fig. 5. Heart rate (top) and stroke volume (bottom) dynamics at the onset of heavy-intensity exercise in a representative age-matched control (left) and a patient with COPD (right). Note that both responses were slower (higher MRT = \( \tau + TD \)) in the COPD patient compared with the control subject. bpm, Beats/min.

![Fig. 6. Changes in \([HbH]\) measured by near-infrared spectroscopy at the onset of heavy-intensity exercise in a representative age-matched control and a patient with COPD. Values are expressed relative to the change of variation found in each test. Note the faster kinetics (lower MRT = \( \tau + TD \)) in the COPD patient, i.e., \( O_2 \) extraction rate was faster in patients than controls.

![Fig. 7. Significant positive relationship between an index of the kinetics of microvascular \( O_2 \) delivery (\( \tau \) of the “primary” component of the on-transient \( V_\text{O}_2p/MRT \) of the changes in \([HbH]\)) and the kinetics of systemic \( O_2 \) delivery, as estimated by the dynamics of \( Q_\text{T} \) (MRT-\( Q_\text{T} \)), at the onset of heavy-intensity exercise in healthy controls and patients with COPD.](http://jap.physiology.org/)}
significantly impaired by abnormal pulmonary-mechanical responses in patients with moderate-to-severe COPD.

**Kinetics of Muscle Oxygenation**

Tissue oxygenation kinetics during exercise are probably the most relevant assessment to determine the effects of COPD on the dynamic supply of O2 in relation to VO2 of the muscle. The finding that [HHb] kinetics were faster than the phase II VO2p and Qt dynamics in both COPD patients and controls is in close agreement with data from previous investigations in young (15, 19, 24) and old adults (15, 16). This appears to stem from differences in the profile of muscle VO2 (monoeponential) and muscle O2 delivery (a biphasic response) (18, 38, 39). The faster increase in [HHb] in patients than controls, an estimate of muscle microvascular O2 extraction kinetics (16, 18, 24), suggests that any cardiovascular dysfunction related to COPD was sufficient to impair the dynamic matching of muscle QO2mV and VO2 during the on-transient phase of heavy exercise (Figs. 3 and 6).

The slowing of Qt reported here is a feasible explanation for the sluggish increase in QO2mV and speeding of [HHb] response. This theory is supported by the close association between the kinetics of Qt and our qualitative index of QO2mV dynamics (rVO2p/MRT[HHb]) (Fig. 7). However, a temporally reduced O2 availability could also be related to impaired muscle microvascular function in response to exercise in patients with COPD, independent of the central cardiovascular dysfunction (see above). Heightened sympathetic vasoconstriction at rest will slow the increase in muscle blood flow (48). Among the known muscle vasodilatory mediators, much emphasis has been given to nitric oxide (NO), especially in disease states. Blockade of NO synthase hastens the increase in O2 extraction in healthy rat muscles (20). Furthermore, it has been demonstrated that conditions associated with vascular endothelial dysfunction and reduced vascular NO availability, such as diabetes (6), aging (9, 46), and heart failure (10), are characterized by slowing of muscle O2 delivery and speeding of the increase in microvascular O2 extraction during contractions. Surprisingly, there is a lack of data on peripheral endothelial function in COPD patients. However, COPD patients are usually former smokers, have increased plasma levels of tumor necrosis factor-α, and reactive oxygen species (as reviewed in Ref. 21). All of these factors will contribute to lower NO availability, predisposing the patients to microvascular dysfunction (55). Therefore, although the sluggish increase in muscle QO2mV may be determined mainly by the central cardiovascular effects of COPD that slows the kinetics of Qt, as suggested by Fig. 7, microvascular dysfunction should not be neglected in these patients.

In our older controls, muscle deoxygenation displayed a slow-component response similar, and directly related, to that observed in VO2p. This is in close agreement with studies in younger subjects (15, 16) and consistent with the notion that most of the slow-component observed in the VO2p response comes from the exercising legs (37). Another interesting finding in the present study was the dissociation between the presence and magnitude of the slow component of VO2p and [HHb] in patients with COPD. While the slow component of VO2p was found in all patients, only four of them showed a similar profile in the [HHb] response. These data might indicate that the determinants of the “extra” VO2p can vary in individual COPD patients. Future studies, for instance, should investigate whether the extra VO2p could be explained, at least partially, by increased ventilatory cost of exercise and/or higher work of breathing at a given ventilation.

**Methodological Considerations**

Due to the noninvasive nature of our study, several methodological aspects need further clarification. First and foremost, we assumed that the kinetics of deoxy-HbMb measured at a single site reflects the time course of muscle microvascular O2 extraction following the onset of exercise. Although there is ongoing controversy regarding the primary determinant of the NIRS signal (31, 47), several studies have used [HHb] from a single site in the quadriceps muscle as a proxy of tissue “fractional” O2 extraction (6, 15, 16, 18, 19, 24) and provided extensive discussion on this topic. A key argument supporting the use of [HHb] as an approximation of O2 extraction dynamics is the generally similar characteristics of [HHb] response in humans (15, 16, 18, 19, 24) compared with O2 extraction dynamics measured in skeletal muscles (9, 10, 23) and calculated in computer simulations (18). In addition, the NIRS technology employed in our study does not allow measurement of tissue-scattering properties. This prevented calculation of absolute values of [HHb], but it is unlikely that it would have affected the kinetics profile of HHb compared with results yielded by measuring scattering and incorporating it in our calculations (31).

Other important issues are the use of data from a single transition to determine differences in VO2p, Qt, and [HHb] kinetics, and assumption that the primary component of VO2p kinetics represents the dynamics of muscle VO2 in COPD patients. Although the use of one transition may limit resolution of small differences in kinetic responses, especially for VO2p and Qt, the differences between COPD and controls were large enough to be detected statistically, as suggested by the study of Puente-Maestu et al. (41). The kinetics of the primary component of VO2p response is widely used as an indicator of the muscle VO2 response, as the time course of the primary component has been shown (24) or predicted (4) to closely reflect (within 10%) the muscle VO2 response. Grassi et al. (24), for instance, found a close similarity between the kinetics of leg VO2 and VO2p during cycling exercise, and Rossiter et al. (43) demonstrated that phosphocreatine breakdown (from 31P-NMR), which is considered to be closely linked to mitochondrial O2 consumption (32), followed a similar dynamic profile to that of the primary component of VO2p during moderate-intensity exercise. However, slowing of muscle blood flow may create a discrepancy between muscle and pulmonary VO2 kinetics, where the VO2p response will become faster than the muscle VO2 dynamics due to changes in the leg-to-lung transit delay (39). Therefore, based on the Qt and [HHb] kinetics determined in our study, we may have underestimated the slowness of muscle VO2 kinetics in patients with COPD performing heavy-intensity exercise.

**Conclusions**

In general, our data show that patients with moderate-to-severe COPD have impaired central and peripheral cardiovascular responses to exercise that lead to slower kinetics of Qt and faster muscle deoxygenation profile following the onset of
heavy-intensity exercise. The latter effects are in opposite direction to that expected to be seen when the slowing of VO2 kinetics occur due only to intrinsic muscle metabolic disturbances, and there is a surplus of O2 delivery to contracting muscles. Our interpretation of the data, therefore, is that derangements in convective O2 delivery to skeletal muscles might contribute substantially to limit the kinetics of VO2p and exercise tolerance during heavy-intensity exercise in patients with moderate-to-severe COPD. However, without knowing the absolute values of microvascular PO2 following the onset of contractions, and if those were low enough to impair O2 transfer from blood to muscle, we cannot establish with certainty that the slouthful kinetics of VO2p in COPD were a consequence of reduced O2 availability. This can be resolved by studies examining the effects of interventions that increase muscle O2 delivery, or speed its dynamics, on the kinetics of VO2 at high-intensity exercise in patients with COPD.

ACKNOWLEDGMENTS

We thank all colleagues from the Pulmonary Function and Clinical Exercise Physiology Unit (Division of Respiratory Diseases, Department of Medicine, Federal University of Sao Paulo, Brazil) for collaborative efforts. We are also grateful to Laura D. Batista for technical support and Diricelene P. Moreira for competent secretarial assistance. More importantly, however, we are indebted to the patients for their effort and enthusiastic cooperation throughout the study.

GRANTS

This study was supported by a Research Grant from Fundação de Amparo à Pesquisa do Estado de São Paulo, São Paulo, Brazil (no. 05/00722-0). G. R. Chiappa is a Postdoctoral Researcher at the Federal University of São Paulo, and J. A. Neder is an Established Investigator (level II) of the Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil.

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