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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1Pulmonary Function and Clinical Exercise Physiology Unit, Division of Respiratory Diseases, Department of Medicine, Federal University of Sao Paulo, Sao Paulo; and 2Cardiopulmonary Laboratory, Nucleus of Research in Physical Exercise, Federal University of Sao Carlos, Sao Carlos, Brazil; and 3Department of Physiology, University of Kentucky, Lexington, Kentucky

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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 pulmonary oxygen uptake (V˙O₂p) kinetics during exercise, which may stem from inadequate muscle O₂ delivery. However, it is currently unknown how COPD impacts the dynamic relationship between systemic and microvascular O₂ delivery to uptake during exercise. We tested the hypothesis that, along with slowed V˙O₂p kinetics, COPD patients have faster dynamics of muscle deoxy-Hb, but slower kinetics of cardiac output (Qt) following the onset of heavy-intensity exercise. We measured V˙O₂p, Qt (impedance cardiography), and muscle deoxygenation (near-infrared spectroscopy) during heavy-intensity exercise performed to the limit of tolerance by 10 patients with moderate-to-severe COPD and 11 age-matched sedentary controls. Variables were analyzed by standard nonlinear regression equations. Time to exercise intolerance was significantly (P < 0.05) lower in patients and related to the kinetics of V˙O₂p (r = −0.70, P < 0.05). Compared with controls, COPD patients displayed slower kinetics of V˙O₂p (42 ± 13 vs. 73 ± 24 s) and Qt (67 ± 11 vs. 96 ± 32 s), and faster overall kinetics of muscle deoxy-Hb (19.9 ± 2.4 vs. 16.5 ± 3.4 s). Consequently, the time constant ratio of O₂ uptake to mean response time of deoxy-Hb concentration was significantly greater in patients, suggesting a slower kinetics of microvascular O₂ delivery. In conclusion, our data show that patients with moderate-to-severe COPD have impaired central and peripheral cardiovascular adjustments following the onset of heavy-intensity exercise. These cardiocirculatory disturbances negatively impact the dynamic matching of O₂ delivery and utilization and may contribute to the slower V˙O₂p kinetics compared with age-matched controls.

blood flow; chronic obstructive pulmonary disease; hemodynamics; near-infrared spectroscopy; oxygen consumption; kinetics

FOLLOWING THE ONSET OF EXERCISE, the dynamic increase in pulmonary oxygen uptake (V˙O₂p) is slowed in patients with chronic obstructive pulmonary disease (COPD) compared with age-matched controls (12, 34, 36, 40, 41, 45). The slowed kinetics of V˙O₂p leads to greater reliance on oxygen-independent metabolic pathways and accumulation of by-products that might be related to increased muscle fatigability (e.g., phosphate and H+). Thus the slow increase in V˙O₂p may be mechanistically associated with the marked decrement in 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 V˙O₂ kinetics in COPD. During moderate-intensity (sub-“lactate threshold”) exercise, the existing literature suggests that V˙O₂ 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 V˙O₂ 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 (Qt, , ) to a greater extent than the rate of O₂ utilization, as indicated by the V˙O₂ 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 V˙O₂ 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 V˙O₂ kinetics being limited by activation of intracellular metabolic pathways (3, 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 QO2,m is associated with the kinetics of Qt (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 steroids 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 pulmonary 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 as 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 anaerobic 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, Medialia, 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 VCO2p with regard to VO2p (modified V-slope) (8) and by the ventilatory method when VE-to-VCO2p 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 NIBO 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-
ical). The PhysioFlow device and its methodology have been thoroughly described elsewhere (13). Before each exercise test, the system was autocalibrated, taking into consideration age, stature, body mass, and blood pressure values. Signal quality was verified by visualizing the ECG tracing and its first derivative and the impedance waveform with its first derivative. In preliminary experiments, the coefficient of variation for changes in QT and SV during exercise were 3.3 and 4.1%, respectively. In these preliminary trials, the changes in QT measured by impedance cardiography were consistent with those predicted from V̇O₂p values using the submaximal Qt-V̇O₂p relationship described in COPD patients (data not shown) (29, 35).

Kinetics Analysis

The breath-by-breath V̇O₂p, SpO₂, NIRS oxygenation, and hemodynamic (Qt, SV, and HR) data were interpolated second by second before kinetics analysis (SigmaPlot 10.0, Systat Software, San Jose, CA). The V̇O₂p responses to exercise in the intensity domain used in our investigation are characterized by the presence of a slow component (34). Therefore, the data relative to the first 20 s after exercise onset, i.e., the exponential response of interest. In the analysis of QT, 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 16, 24) suggest the primary phase of the HHb response is complete analyzed (15, 16, 18, 19). Theoretical (18) and empirical studies (15, 16) minimize distortion of the curve-fitting seen when longer periods are course of the primary component of the response, an estimate of the TDp was dropped from the equation. For V̇O₂p analysis, we deleted the TDp was estimated as the change from 3 min to the end of exercise (end-3)

\[ [\text{HHb}]_{\text{corr}} = [\text{HHb}] - (1 - \text{SpO}_2) \times [\text{HHb}] \]  

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

\[ Y(t) = Y_0 + A \cdot e^{-(t - \tau)/T_D} \]  

where [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 τ is time constant of the exponential response of interest. In the analysis of Qt, 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, τpV̇O₂p represents the time course of the primary component of the response, an estimate of the muscle V̇O₂ 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 = τ + TD). In addition, the amplitude of the "slow component" of V̇O₂p, Qt, and [HHb] was estimated as the change from 3 min to the end of exercise (end-3) (39).

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, Qt, 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, VE-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, VE-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 Qt are shown in Figs. 1 and 2, respectively. The dynamics of V̇O₂p were slower in patients than controls (Table 3, Fig. 3). In asub-

Table 1. Resting characteristics of normal controls and patients with COPD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Age, yr</td>
<td>61.4±6.3</td>
<td>59.8±7.9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.3±5.0</td>
<td>25.1±2.2</td>
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</table>

Demographical/anthropometric

<table>
<thead>
<tr>
<th>Pulmonary function</th>
<th>Controls</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, liters</td>
<td>3.31±0.50</td>
<td>1.05±0.58*</td>
</tr>
<tr>
<td>FEV₁, %predicted</td>
<td>99.6±9.4</td>
<td>44.0±15.8*</td>
</tr>
<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>105.9±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>PacO₂, Torr</td>
<td>72±7</td>
<td>94±2</td>
</tr>
<tr>
<td>PacO₂, %</td>
<td>38±5</td>
<td></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; PacO₂ and PacCO₂, arterial PO₂ and PCO₂, 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 (Fig. 5). The dynamics of both variables were significantly COPD patients, we evaluated the kinetics of HR and SV of the latter as an estimate of muscle microvascular $O_2$ delivery.

Values are means ± SD with the exception of symptoms (median and range); $n$, no. of subjects. $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; RER, respiratory exchange rate; GET, gas exchange threshold; $V_t$, minute ventilation; MVV, maximal voluntary ventilation; $Sp_o_2$, oxyhemoglobin saturation by pulse oximetry. *$P < 0.05$ (between-group differences in a given exercise testing protocol).

group of subjects in whom the tests were repeated (4 patients and 5 controls), the coefficient of variation for $\tau\dot{V}O_2p$ averaged 6.8 and 8.4%, respectively. There was a significant inverse relationship between $\tau\dot{V}O_2p$ and $T_{lim}$ in COPD patients ($r = -0.70, P < 0.01$; Fig. 4) and when data from all subjects were pooled together ($r = -0.56, P < 0.05$). As expected, a $\dot{V}O_2p$ “slow” component was found in all subjects ($P < 0.05$). There were no between-group differences in the magnitude of the $\dot{V}O_2$ slow component $[\Delta\dot{V}O_2p_{(end-3')] = 202 ± 99$ vs. $185 ± 89$ ml/min for patients and controls, respectively], and the relationship between $\Delta\dot{V}O_2p_{(end-3')]$ and $T_{lim}$ was not significant in either group ($P > 0.05$).

The increase in $\dot{Q}T$ was slower in patients compared with controls and longer than those of $\dot{V}O_2p$ in both groups (Table 3, Fig. 3). To gain further insights into the slowing of $\dot{Q}T$ of patients compared with controls ($4.9 ± 1.2$ vs. $2.5 ± 0.6$, respectively; $P < 0.01$), suggesting that $Q_{O_2_{mv}}$ adapted at a slower rate in patients. Interestingly, $Q_{O_2_{mv}}$ was closely related to MRT-$\dot{Q}T$ (Fig. 7), suggesting that the dynamics of $Q_{O_2_{mv}}$ 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 $\dot{V}O_{2p}$, $\dot{Q}T$, 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-$\dot{V}O_2p$ are impaired by COPD and set the stage for future interventional studies. We found that $\dot{V}O_{2p}$ 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 $\dot{Q}T$ and faster dynamics of $[HHb]$. Interpretation of the latter as an estimate of muscle microvascular $O_2$ extraction suggests that the dynamics of muscle $Q_{O_2_{mv}}$ were slower in COPD patients. Accordingly, a qualitative index of $Q_{O_2_{mv}}$ kinetics (ratio of $\tau\dot{V}O_{2p}$ to MRT-$[HHb]$) was greater in COPD patients and was closely related to the overall kinetics of $\dot{Q}T$. 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.

Table 2. Physiological and perceptual responses at peak incremental and constant work rate exercise cessation in controls and patients with COPD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Incremental Exercise</th>
<th></th>
<th>Constant Work Rate Exercise</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>COPD</td>
<td>Controls</td>
<td>COPD</td>
</tr>
<tr>
<td>$n$</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Power, W</td>
<td>130±15</td>
<td>91±24*</td>
<td>95±17 W</td>
<td>70±16*</td>
</tr>
<tr>
<td>$\dot{V}O_2$, 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>$\dot{V}CO_2$, ml/min</td>
<td>1,860±343</td>
<td>1,427±330*</td>
<td>1,490±298</td>
<td>1,227±303*</td>
</tr>
<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>
</tr>
<tr>
<td>$\dot{V}O_2$ at the GET, ml/min</td>
<td>2.12±0.21</td>
<td>1.008±174*</td>
<td>---</td>
<td>1.21</td>
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<tr>
<td>$V_t$, l/min</td>
<td>67.2±13.9</td>
<td>43.8±9.4*</td>
<td>53.8±11.7</td>
<td>41.7±10.8*</td>
</tr>
<tr>
<td>$V_t$/MVV</td>
<td>0.35±0.08</td>
<td>0.88±0.10*</td>
<td>0.30±0.06</td>
<td>0.86±0.09*</td>
</tr>
<tr>
<td>Heart rate, %predicted</td>
<td>88±9.8</td>
<td>82.5±9.6</td>
<td>78.4±8.7</td>
<td>75.3±10.1</td>
</tr>
<tr>
<td>$Sp_o_2, %$</td>
<td>95±4</td>
<td>92±3</td>
<td>94±4</td>
<td>92±2</td>
</tr>
<tr>
<td>Dyspnea score</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 score</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>

$\dot{V}O_2$, $\dot{V}CO_2$, $\dot{Q}T$, and $T_{lim}$ were not significant if key determinants of the dynamic matching of central and peripheral (microvascular) $O_2$ delivery-to-$\dot{V}O_2p$ are impaired by COPD and set the stage for future interventional studies. We found that $\dot{V}O_{2p}$ 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 $\dot{Q}T$ and faster dynamics of $[HHb]$. Interpretation of the latter as an estimate of muscle microvascular $O_2$ extraction suggests that the dynamics of muscle $Q_{O_2_{mv}}$ were slower in COPD patients. Accordingly, a qualitative index of $Q_{O_2_{mv}}$ kinetics (ratio of $\tau\dot{V}O_{2p}$ to MRT-$[HHb]$) was greater in COPD patients and was closely related to the overall kinetics of $\dot{Q}T$. 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.
V˙O\textsubscript{2p} Kinetics and Tolerance to Heavy-intensity Exercise

Several groups have reported that V˙O\textsubscript{2p} kinetics are slowed by healthy aging (9, 11, 15, 16), and this could be due to impairments in the dynamics of \(\text{O}_2\) delivery (15, 16). In general, data from our control group describing the kinetics of V˙O\textsubscript{2p} and central cardiovascular responses to heavy exercise are in close agreement with previous studies (9, 11, 15, 16). In COPD patients, the kinetics of V˙O\textsubscript{2p} during moderate-intensity (sublactate threshold) exercise are \(45\text{–}65\%\) slower than in healthy aged controls (34, 36, 40). We extended these findings to show that V˙O\textsubscript{2p} kinetics during heavy-intensity exercise were, on average, \(74\%\) slower in COPD patients (Table 3). Moreover, phase II V˙O\textsubscript{2p} 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 T\text{lim} during moderate exercise and the decrease in \(\tau\text{V}_\text{O2p}\) 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 V˙O\textsubscript{2p} 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 V˙O\textsubscript{2p} Kinetics at Heavy-intensity Exercise in COPD

The factors generally considered as limiting the kinetics of V\textsubscript{O2} are the adequacy of \(\text{O}_2\) delivery during the transient phase following the onset of exercise (27) and/or the activity of intracellular biochemical reactions that stimulate mitochondrial V\textsubscript{O2}, also called “metabolic inertia” (23). Several groups emphasize the role of \(\text{O}_2\) delivery limitation to V\textsubscript{O2} kinetics in the elderly (9, 15, 16) and in chronic diseases (5, 6, 10). The argument for \(\text{O}_2\) delivery limitation of V\textsubscript{O2} 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 V\textsubscript{O2} (18). Moreover, interventions that appear to increase muscle oxygenation promoted a speeding of V\textsubscript{O2p} kinetics in the elderly (15). If derangements in \(\text{O}_2\) delivery explain, at least partially, the slowing of V\textsubscript{O2} kinetics with healthy aging, it is conceivable that any pathological condition that could further slow the

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**Fig. 1. Pulmonary O\textsubscript{2} uptake (V\textsubscript{O2p}) 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 (\(\tau\)) of the “primary” component] in the COPD patient compared with the control subject.

**Fig. 2. Cardiac output (Q\text{t}) 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) = \(\tau\) + 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 V̇O₂p during heavy-intensity exercise. However, to elucidate the main determinant of slower V̇O₂p 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 V̇O₂p kinetics in COPD patients. Consistent with this notion, V̇O₂p 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 V̇O₂p with no effect on HR dynamics, which is usually considered an indicator of Q̇T (and O2 delivery) kinetics (12). Thus, in lieu of similar O2 delivery following the onset of heavy-breathing (45), which was assumed to increase muscle O2 delivery. Moreover, exercise training speeded the kinetics of V̇O₂p with no effect on HR dynamics, which is usually considered an indicator of Q̇T (and O2 delivery) kinetics (12). Thus, in lieu of similar O2 delivery following the onset of heavy-breathing (45), which was assumed to increase muscle O2 delivery. Moreover, exercise training speeded the kinetics of V̇O₂p with no effect on HR dynamics, which is usually considered an indicator of Q̇T (and O2 delivery) kinetics (12). Thus, in lieu of similar O2 delivery following the onset of heavy-breathing (45), which was assumed to increase muscle O2 delivery. Moreover, exercise training speeded the kinetics of V̇O₂p with no effect on HR dynamics, which is usually considered an indicator of Q̇T (and O2 delivery) kinetics (12). Thus, in lieu of similar O2 delivery following the onset of heavy-breathing (45), which was assumed to increase muscle O2 delivery.

Potential explanations for slower on-transient Q̇T (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 Q̇T dynamics. Regarding the SV response, the deleterious cardio-circulatory consequences of increasing

**Table 3. Kinetic parameters of V̇O₂p, Q̇t, and [HHb] for controls and patients with COPD**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls Baseline</th>
<th>Controls A</th>
<th>Controls TD</th>
<th>COPD Baseline</th>
<th>COPD A</th>
<th>COPD TD</th>
<th>Controls [HHb]</th>
<th>COPD [HHb]</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇O₂p</td>
<td>521±100</td>
<td>6.4±1.5</td>
<td>6.5±5.0</td>
<td>510±110</td>
<td>7.8±1.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Q̇t</td>
<td>865±156</td>
<td>5.4±2.3</td>
<td>7.2±12.9</td>
<td>691±250</td>
<td>6.4±2.3</td>
<td>96.2±31.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TD</td>
<td>42.1±12.9</td>
<td>66.6±10.8</td>
<td>3.2±10.3</td>
<td>7.29±23.3*</td>
<td>96.2±31.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6.5±5.0</td>
<td>7.2±12.9</td>
<td>3.2±10.3</td>
<td>7.8±7.7</td>
<td>9.8±1.4</td>
<td>6.7±1.2*</td>
<td>9.2±3.2</td>
<td>10.3±3.9</td>
</tr>
</tbody>
</table>

Values are means ± SD. V̇O₂p, pulmonary V̇O₂; Q̇T, 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 V̇O₂p, Q̇T, 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 V̇O₂p and Q̇T 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 V̇O₂p vs. Q̇T and [HHb]; ‡P < 0.05 for within-group comparisons of Q̇T 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 V̇O₂p 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˙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˙O2p kinetics compared with control values, suggesting that alterations in the mechanics of breathing can reduce muscle O2 delivery enough to affect the kinetics of V˙O2p.

Another relevant mechanism for a reduced O2 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 Qr. Considering that some patients seem to recruit massively the abdominal muscles (2), it is conceivable that these adjustments could impair peripheral O2 delivery. Moreover, respiratory muscle work during heavy exercise can divert a fraction of the Qr 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 Qr 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 O2 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 = τ + TD) in the COPD patient compared with the control subject. bpm, Beats/min.

Fig. 6. Changes in [HHb] 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 = τ + TD) in the COPD patient, i.e., O2 extraction rate was faster in patients than controls.

Fig. 7. Significant positive relationship between an index of the kinetics of microvascular O2 delivery (τ of the “primary” component of the on-transient V˙O2p/MRT of the changes in [HHb]) and the kinetics of systemic O2 delivery, as estimated by the dynamics of Qr (MRT-Qr), at the onset of heavy-intensity exercise in healthy controls and patients with COPD.
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 V\textsubscript{O2} of the muscle. The finding that [HHb] kinetics were faster than the phase II V\textsubscript{O2p} and Q\textsubscript{T} 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 \( \text{V}_2 \) (monoeponential) and muscle \( \text{O}_2 \) delivery (a biphasic response) (18, 38, 39). The faster increase in [HHb] in patients than controls, an estimate of muscle microvascular \( \text{O}_2 \) extraction kinetics (16, 18, 24), suggests that any cardiovascular dysfunction related to COPD was sufficient to impair the dynamic matching of muscle Q\textsubscript{O2m} and \( \text{V}_2 \) during the on-transient phase of heavy exercise (Figs. 3 and 6).

The slowing of Q\textsubscript{T} reported here is a feasible explanation for the sluggish increase in Q\textsubscript{O2m} and speeding of [HHb] response. This theory is supported by the close association between the kinetics of Q\textsubscript{T} and our qualitative index of Q\textsubscript{O2m} dynamics (\( r\text{V}_2/\text{MRT}[\text{HHb}] \)) (Fig. 7). However, a temporally reduced \( \text{O}_2 \) 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 \( \text{O}_2 \) 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 \( \text{O}_2 \) delivery and speeding of the increase in microvascular \( \text{O}_2 \) 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-\( \alpha \), 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 Q\textsubscript{O2m} may be determined mainly by the central cardiovascular effects of COPD that slows the kinetics of Q\textsubscript{T}, 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 V\textsubscript{O2p}. 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 V\textsubscript{O2p} 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 V\textsubscript{O2p} and [HHb] in patients with COPD. While the slow component of V\textsubscript{O2p} 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" V\textsubscript{O2p} can vary in individual COPD patients. Future studies, for instance, should investigate whether the extra V\textsubscript{O2p} 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-Hb/Mb measured at a single site reflects the time course of muscle microvascular \( \text{O}_2 \) 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" \( \text{O}_2 \) 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 \( \text{O}_2 \) extraction dynamics is the generally similar characteristics of [HHb] response in humans (15, 16, 18, 19, 24) compared with \( \text{O}_2 \) 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 V\textsubscript{O2p}, Q\textsubscript{T}, and [HHb] kinetics, and assumption that the primary component of V\textsubscript{O2p} kinetics represents the dynamics of muscle \( \text{V}_2 \) in COPD patients. Although the use of one transition may limit resolution of small differences in kinetic responses, especially for V\textsubscript{O2p} and Q\textsubscript{T}, 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 V\textsubscript{O2p} response is widely used as an indicator of the muscle \( \text{V}_2 \) response, as the time course of the primary component has been shown (24) or predicted (4) to closely reflect (within 10%) the muscle \( \text{V}_2 \) response. Grassi et al. (24), for instance, found a close similarity between the kinetics of leg \( \text{V}_2 \) and V\textsubscript{O2p} during cycling exercise, and Rossiter et al. (43) demonstrated that phosphocreatine breakdown (from \( \text{P}_2 \)-NMR), which is considered to be closely linked to mitochondrial \( \text{O}_2 \) consumption (32), followed a similar dynamic profile to that of the primary component of V\textsubscript{O2p} during moderate-intensity exercise. However, slowing of muscle blood flow may create a discrepancy between muscle and pulmonary \( \text{V}_2 \) kinetics, where the V\textsubscript{O2p} response will become faster than the muscle \( \text{V}_2 \) dynamics due to changes in the leg-to-lung transit delay (39). Therefore, based on the Q\textsubscript{T} and [HHb] kinetics determined in our study, we may have underestimated the slowness of muscle \( \text{V}_2 \) 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 Q\textsubscript{T} 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 \( \dot{V}O_2 \) kinetics occur due only to intrinsic muscle metabolic disturbances, and there is a surplus of \( O_2 \) delivery to contracting muscles. Our interpretation of the data, therefore, is that derangements in convective \( O_2 \) delivery to skeletal muscles might contribute substantially to limit the kinetics of \( \dot{V}O_2 \) and exercise tolerance during heavy-intensity exercise in patients with moderate-to-severe COPD. However, without knowing the absolute values of microvascular \( P_O2 \) following the onset of contractions, and if those were low enough to impair \( O_2 \) transfer from blood to muscle, we cannot establish with certainty that the slowthful kinetics of \( \dot{V}O_2 \) in COPD were a consequence of reduced \( O_2 \) availability. This can be resolved by studies examining the effects of interventions that increase muscle \( O_2 \) delivery, or speed its dynamics, on the kinetics of \( \dot{V}O_2 \) at high-intensity exercise in patients with COPD.

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