Effect of Hyperoxia on Gas Exchange and Lactate Kinetics Following Exercise Onset in Nonhypoxemic COPD Patients*

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Study objectives: The slow oxygen uptake (Vo2) kinetics observed in COPD patients is a manifestation of skeletal muscle dysfunction of multifactorial origin. We determined whether oxygen supplementation during exercise makes the dynamic Vo2 response faster and reduces transient lactate increase.

Design: Ten patients with severe COPD (ie, mean [± SD] FEV1, 31 ± 10% predicted) and 7 healthy subjects of similar age performed four repetitions of the transition between rest and 10 min of moderate-intensity, constant-work rate exercise while breathing air or 40% oxygen in random order. Minute ventilation (Ve), gas exchange, and heart rate (HR) were recorded breath-by-breath, and arterialized venous pH, PCO2, and lactate levels were measured serially.

Results: Compared to healthy subjects, the time constants (τ) for Vo2, HR, carbon dioxide output (VCO2), and Ve kinetic responses were significantly slower in COPD patients than in healthy subjects (70 ± 8 vs 44 ± 3 s, 98 ± 14 vs 44 ± 8 s, 86 ± 8 vs 61 ± 4 s, and 81 ± 7 vs 62 ± 4 s, respectively; p < 0.05). Hyperoxia decreased end-exercise Ve in the COPD group but not the healthy group. Hyperoxia did not increase the speed of Vo2 kinetics but significantly slowed VCO2 and Ve response dynamics in both groups. Only small increases in lactate occurred with exercise, and this increase did not correlate with the τ for Vo2.

Conclusion: In nonhypoxemic COPD patients performing moderate exercise, the lower ventilatory requirement induced by oxygen supplementation is not related to improved muscle function but likely stems from direct chemoreceptor inhibition.

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Key words: COPD; exercise; gas exchange kinetics; lactate; muscle dysfunction; oxygen

Abbreviations: HR = heart rate; LAT = lactic acidosis threshold; SpO2 = O2 saturation measured by pulse oximetry; VCO2 = carbon dioxide output; Ve = minute ventilation; Ve/VCO2 = ventilatory equivalent for CO2; Vo2 = oxygen uptake

We recently demonstrated1 that supplemental oxygen substantially increased the exercise tolerance of patients with COPD who manifest mild arterial oxygen desaturation during exercise. The degree of exercise endurance enhancement produced by oxygen breathing was correlated with the reduction in ventilatory requirement for exercise. It was hypothesized that the reduced ventilatory requirement enabled the prolongation of the time for exhalation and, therefore, yielded less hyperinflation. Dynamic hyperinflation has been postulated to be a dominant mechanism of exercise tolerance limitation in COPD patients.2

However, the benefits of oxygen are multifactorial. We can conceive of three beneficial effects of oxygen therapy that potentially might increase exercise tolerance: (1) pulmonary vasodilation, which might allow increased cardiac output; (2) increased oxyhemoglobin saturation, which would increase arterial oxygen content; and (3) increased arterial PO2, which could inhibit carotid chemoreceptor discharge. The first two mechanisms would succeed in decreasing the ventilatory requirement for exercise only if oxygen delivery to the exercising muscles was thereby increased and aerobic metabolism was facilitated.
COPD patients have been found to have dysfunctional muscles, and one manifestation of this dysfunction is the onset of lactic acidosis at low work rates. Improved muscle oxygen delivery has the potential to ameliorate lactic acidosis and, thereby, to reduce ventilatory stimulation. Furthermore, muscle fatigue, in itself, may be a contributing factor to exercise limitation in COPD patients so it is plausible that improved muscle oxygen delivery may directly alter muscle acidosis and the perception of fatigue.

A key piece of evidence suggesting that the muscles of ambulation of patients with COPD do not function normally is the slowness of oxygen uptake (VO₂) kinetics following the onset of moderate exercise. Morphologic studies have revealed a reduction in the proportion of oxidative (type I) fibers accompanied by an increase of glycolytic (type II) fibers of the vastus lateralis muscle in COPD patients. The lower number of capillary contacts for fibers of the vastus lateralis muscle in COPD patients is overbalanced by the vasoconstrictor effect of oxygen on the microvasculature of skeletal muscle is overbalanced by the vasoconstrictor effect of oxygen on the microvasculature increases muscle oxygen delivery. That is, the onset considerably, resulting in a smaller oxygen diffusion in the proportion of oxidative (type I) fibers and the reduced myoglobin production in the proportion of oxidative (type I) fibers and the reduced myoglobin content of skeletal muscles also suggests inefficient oxygen utilization. These factors likely contribute to slow VO₂ kinetics, resulting in an increased oxygen deficit. Such an oxygen deficit would be expected to elicit transient reliance on anaerobic energy sources; this has been shown to be associated with an "early lactate" response (ie, a transient elevation in lactate level even for exercise below the anaerobic threshold).

Information relevant to determining whether supplemental oxygen therapy improves the aerobic function of the exercising muscles was obtained by Palange et al. They found that, in COPD patients with only mild desaturation, breathing 30% oxygen speeded the VO₂ response to moderate exercise onset considerably, resulting in a smaller oxygen deficit. This finding implies, first, that oxygen breathing increases muscle oxygen delivery. That is, the vasoconstrictor effect of oxygen on the microvasculature of skeletal muscle is overbalanced by the higher oxygen content in the arterial blood. Second, this finding implies that muscle oxygen metabolism early in exercise is oxygen flow-limited and that higher oxygen supply ameliorates the transient reliance on anaerobic energy sources, thus reducing oxygen debt.

To better define the consequences of oxygen supplementation on muscle metabolism at the onset of moderate-intensity exercise in COPD patients, we compared VO₂ kinetics while subjects breathed air or 40% oxygen. We sampled blood at frequent intervals during the transition in order to define the kinetic response of blood lactate, hypothesizing that any increase in the speed of VO₂ kinetics produced by oxygen supplementation would be accompanied by a reduced transient rise in blood lactate level. These responses were compared to those of healthy subjects of similar ages.

We also wished to examine the acid-base changes that occur at the onset of exercise in these patients. We, and others, have observed that both carbon dioxide output (VCO₂) and minute ventilation (VE) kinetics are slow in COPD patients performing moderate exercise and that these kinetics are slowed further by breathing oxygen. We reasoned that the transient behavior of PCO₂ and pH in the arterialized venous blood of COPD patients, in comparison to that observed in healthy subjects, would help to explain the physiologic mechanisms underlying these observations.

**Materials and Methods**

**Subjects**

We studied 10 clinically stable patients with severe COPD (ie, FEV₁, < 40% of predicted) who were no more than mildly hypoxemic (ie, O₂ saturation measured by pulse oximetry [SpO₂] at rest, > 92%; and SpO₂ during incremental exercise, > 89%). None of these individuals had previously qualified for ambulatory oxygen therapy. Exclusion criteria included clinically manifest cor pulmonale, severe cardiovascular comorbidity, or other disease that might contribute to dyspnea or exercise limitation. Seven healthy volunteers of similar age were also recruited. The characteristics of the participants are listed in Table 1. The institutional review board approved the protocol, and subjects gave written informed consent.

**Study Design**

A randomized, single-blinded, controlled study was designed. All subjects previously had been familiarized with exercise testing. Based on a symptom-limited incremental cycle ergometer exercise test performed while the subjects breathed room air (described below), a constant work rate of moderate intensity equal to 80% of the lactic acidosis threshold (LAT) was selected. During the constant-work rate tests, subjects breathed compressed air or 40% oxygen in randomized order. Subjects were blinded with respect to the oxygen concentration being inhaled. Four transitions from rest to exercise were performed in each experimental condition. The study was designed with four visits, each separated by 3 to 5 days. Each study day consisted of two exercise tests, one with room air and one with 40% oxygen breathing, with an intervening 1-h recovery period. Subjects avoided caffeine, alcohol, or heavy meals before testing. Patients took their prescribed bronchodilator medications prior to testing.

**Pulmonary Function Testing**

Before exercise testing, subjects underwent pulmonary function testing (Vmax 229 and Autobox 6200; SensorMedics; Yorba Linda, CA) including spirometry, lung volumes determined by plethysmography, and single-breath carbon monoxide diffusing capacity. The normal values were those given in the work of Knudson et al., Goldman and Becklake, and Crapo and...
A symptom-limited incremental exercise test was conducted with the subject breathing room air on an electronically braked cycle ergometer (Ergoline-800; SensorMedics). After 3 min of rest and 3 min of unloaded pedaling, the work rate was increased continuously (ramp pattern) by 5 or 10 W/min for the patients and 15 or 20 W/min for the healthy subjects. The peak \( \dot{V}\text{O}_2 \) was determined as the average \( \dot{V}\text{O}_2 \) over the last 30 s of exercise. Constant-work rate tests at a work rate equal to 80% of the LAT were performed on the same ergometer. LAT was determined by the modified V-slope method. The pedaling rate was kept constant between 55 and 65 revolutions per minute. Compressed air and oxygen were blended (air-oxygen blender; SensorMedics) from gas cylinders into a 200-L meteorological balloon to be inspired during exercise. Subjects breathed through a mouthpiece attached to a low-resistance, two-way, nonrebreathing valve (dead space, 80 mL) [Hans-Rudolph; Kansas City, MO] with a nose clip in place. Respiratory flow rates were measured with a calibrated mass flow sensor (SensorMedics). \( \dot{V}\text{E} \), \( \dot{V}\text{O}_2 \), and \( \dot{V}\text{CO}_2 \) were measured breath-by-breath with a metabolic cart (Vmax 29c; SensorMedics). Each test consisted of 3 min of motionless rest followed by 10 min of the assigned constant work rate. To eliminate the initial inertia of the ergometer, 10 s before the beginning of exercise a laboratory staff member manually turned the pedals at 60 revolutions per minute. Equipment was calibrated immediately before each test with a 3-L syringe and two precision gas mixtures. A metabolic pump calibrator, which simulated known levels of \( \dot{V}\text{E} \), \( \dot{V}\text{O}_2 \), and \( \dot{V}\text{CO}_2 \), was also employed. Biological calibration by healthy individuals chosen from among the laboratory personnel with repeated bouts of moderate constant-work rate exercise with 40% oxygen and air breathing revealed (mean ± SD) 8.0 ± 1.7% higher values for \( \dot{V}\text{O}_2 \) during \( \dot{V}\text{O}_2 \) breathing compared to air breathing but no significant differences for \( \dot{V}\text{CO}_2 \) or \( \dot{V}\text{E} \) (-2.6 ± 4.3% and 1.3 ± 3.5%, respectively). The \( \dot{V}\text{O}_2 \) difference was presumed to be related to nonlinearities in the oxygen analyzer at higher fraction of inspired oxygen. \( \dot{V}\text{O}_2 \) values during oxygen breathing were corrected for this error. Heart rate (HR) and oxygen saturation were recorded with continuous ECG (Cardiosoft; SensorMedics) and pulse oximetric (N-200 pulse oximeter; Nellcor; Hayward, CA) monitoring.

On one of the experimental days, before the constant-work rate exercise tests were performed, a 21-gauge butterfly catheter was placed in a vein in the dorsum of the hand. The catheter was flushed intermittently with heparinized saline solution. A heat lamp was used to warm the hand and thereby to arterialize the venous samples. This procedure yielded \( \text{PCO}_2 \), pH, and lactate levels that approximated arterial values. Samples were taken within 60 s after the onset of exercise and at 20, 40, 60, 80, 100, and 120 s and 3, 4, 5, 7, and 10 min after the onset of exercise. Blood samples were taken anaerobically in heparinized syringes and were iced immediately. Each sample was analyzed within 30 min after exercise for \( \text{pH} \) and \( \text{PCO}_2 \) levels (model 1640; Instrumentation Laboratories; Lexington, MA) and, after centrifugation, for plasma lactate (model 2300; Yellow Springs Instruments; Yellow Springs, OH).

### Analysis of Response Kinetics

Before the start of exercise, a sufficient time (10 to 15 min) was allowed for the subjects to accommodate to the mouthpiece and equilibrate gas stores with the inspired air. Further, subjects with COPD were encouraged to take deep breaths intermittently during the initial 7 to 10 min of oxygen breathing in order to equilibrate poorly ventilated airspace. In preliminary studies, we found that achieving the complete equilibrium of lung gas stores was of utmost importance because, otherwise, the deep breathing that occurred at the onset of exercise would tend to wash out the nitrogen in poorly ventilated areas, falsely elevating the \( \dot{V}\text{E} \) levels that approximated arterial values. Samples were taken within 60 s after the onset of exercise and at 20, 40, 60, 80, 100, and 120 s and 3, 4, 5, 7, and 10 min after the onset of exercise. Blood samples were taken anaerobically in heparinized syringes and were iced immediately. Each sample was analyzed within 30 min after exercise for \( \text{pH} \) and \( \text{PCO}_2 \) levels (model 1640; Instrumentation Laboratories; Lexington, MA) and, after centrifugation, for plasma lactate (model 2300; Yellow Springs Instruments; Yellow Springs, OH).

#### Table 1—Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>COPD Patients</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65 ± 7</td>
<td>67 ± 6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 ± 11</td>
<td>172 ± 10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69 ± 12</td>
<td>72 ± 14</td>
</tr>
<tr>
<td>Gender, No.</td>
<td>Male 6</td>
<td>Female 4</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>FVC L</td>
<td>FEV/预计FVC %</td>
</tr>
<tr>
<td></td>
<td>0.92 ± 0.43</td>
<td>76 ± 15</td>
</tr>
<tr>
<td></td>
<td>31 ± 10</td>
<td>107 ± 12</td>
</tr>
<tr>
<td></td>
<td>2.87 ± 0.60</td>
<td>74 ± 9</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD. TLC = total lung capacity; RV = residual volume; DLCO = diffusing capacity of the lung for carbon monoxide, CPX = incremental cardiopulmonary exercise; %MVV = maximum voluntary ventilation.
Healthy Subjects

Comparison between the responses breathing air and oxygen and between COPD patients and healthy subjects were made by paired and unpaired t tests. The correlation among variables was determined by calculating the Pearson product-moment correlation coefficient. Significance was accepted at the p < 0.05 level. Dispersion about the mean values is expressed as ± SD, unless otherwise specified.

RESULTS

The anthropometric variables did not differ significantly between the two groups (Table 1). Pulmonary function was normal in the healthy individuals, while severe airway obstruction and moderate hyperinflation were present in the COPD patients. Peak work rate and peak VO₂ levels were threefold and twofold higher in the healthy subjects, respectively. As gauged by the breathing reserve (ie, the difference between maximum voluntary ventilation [estimated as FEV₁ times 40] and peak exercise ventilation in the incremental test), the COPD patients but not the healthy subjects reached a ventilatory limitation (3.4 ± 1.8 and 41.7 ± 9.2 L/min, respectively). The exercise level for the constant-work rate tests averaged 21 ± 2 W (41 ± 2% of the peak work rate) for the COPD patients and 48 ± 6 W (35 ± 3% of the peak work rate) for the healthy subjects. The variables characterizing gas-exchange and cardiorespiratory response kinetics (which were determined by fitting the response data to our equation) are shown in Table 2. Apart from the mildly higher resting HR values in COPD patients (during both air and oxygen breathing), all preexercise values were similar in the two groups and did not differ significantly between the two inhalations.

As a result of exercising at a higher work rate, the rest-to-steady state exercise response amplitudes for VO₂ and VCO₂ were significantly higher in the healthy subjects than in the COPD patients. The tendency toward a higher HR amplitude failed to achieve statistical significance. In contrast, VE amplitudes were similar in the two groups, which likely was a result of higher dead space ventilation in the COPD patients.

VO₂ time constants were substantially longer in the COPD group, and oxygen supplementation did not result in acceleration of the kinetic response in either group. This finding is reinforced in Figure 2, which shows the grand average of the time courses of responses from all subjects. The VO₂ time courses are essentially identical for air and oxygen breathing in the two groups. Oxygen breathing yielded a mild acceleration in HR kinetics in the COPD group, which failed to achieve statistical significance. The τ values for VCO₂ and VE were significantly greater in the COPD patients. Oxygen breathing resulted in a significant prolongation of these kinetic responses in both groups.

The time courses of change in ventilation, breathing pattern, end-tidal Pco₂ level, ventilatory equivalent for CO₂ (Ve/VCO₂), blood gas composition, and blood lactate level are shown in Figures 3 and 4. The most obvious effect of oxygen was manifested in the pulmonary ventilation and breathing pattern re-

Data Analysis

### Table 2—Oxygen Effect on Response Kinetics

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD Patients</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂, mL/min</td>
<td>Air</td>
<td>40% O₂</td>
</tr>
<tr>
<td>Rest</td>
<td>320 ± 21</td>
<td>322 ± 19</td>
</tr>
<tr>
<td>Amplitude</td>
<td>409 ± 38</td>
<td>411 ± 33</td>
</tr>
<tr>
<td>τ, s</td>
<td>70 ± 8</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>85 ± 2</td>
<td>81 ± 2</td>
</tr>
<tr>
<td>Amplitude</td>
<td>18 ± 3</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>τ, s</td>
<td>98 ± 14</td>
<td>77 ± 16</td>
</tr>
<tr>
<td>VCO₂, mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>268 ± 15</td>
<td>266 ± 20</td>
</tr>
<tr>
<td>Amplitude</td>
<td>379 ± 40</td>
<td>384 ± 37</td>
</tr>
<tr>
<td>τ, s</td>
<td>86 ± 8</td>
<td>129 ± 9</td>
</tr>
<tr>
<td>VE, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>13.1 ± 0.6</td>
<td>12.7 ± 0.9</td>
</tr>
<tr>
<td>Amplitude</td>
<td>12.4 ± 1.6</td>
<td>11.3 ± 1.4</td>
</tr>
<tr>
<td>τ, s</td>
<td>81 ± 7</td>
<td>111 ± 7</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD.

†p < 0.05 vs healthy subjects during identical fraction of inspired oxygen.

‡p < 0.05 vs air.
responses. Breathing 40% oxygen resulted in a slower rise in ventilation, tidal volume, and breathing frequency in the COPD patients, but not in the healthy subjects. The end-exercise $V_{E}$ level was significantly lower during hyperoxia than during normoxia in the COPD patients (25.6 ± 1.9 vs 23.9 ± 1.8 L/min, respectively; $p < 0.05$) but did not differ significantly in the control subjects. The partial pressure of end-tidal CO$_2$ at rest was significantly lower in the COPD patients than in the healthy subjects both while breathing air (34.6 ± 0.7 vs 40.2 ± 0.8 mm Hg, respectively; $p < 0.001$) and breathing oxygen.
Compared to air breathing, oxygen breathing resulted in a significantly greater increase in partial pressure of end-tidal CO2 by the end of exercise both in the COPD group (5.4 ± 0.9 vs 3.3 ± 0.4 mm Hg, respectively; p < 0.001) and in healthy individuals (4.5 ± 0.5 vs 3.0 ± 0.4 mm Hg, respectively; p < 0.001); the magnitude of this elevation during oxygen breathing was significantly (p < 0.001) greater in the COPD patients. The Ve/VCO2 at rest was higher in the COPD group than in the healthy group both while breathing room air (48.7 ± 2.2 vs 38.0 ± 1.5, respectively; p < 0.001) and breathing 40% oxygen (47.1 ± 1.4 vs 39.1 ± 2.3, respectively; p < 0.001). The magnitude of decrease in Ve/VCO2 with exercise (rest to steady-state) was not statistically different between the two groups for a given inhalation.

In the healthy subjects, the levels of end-exercise arterialized venous PCO2 and pH were not statistically different from resting levels during either the air or oxygen studies. In contrast, in the 40% oxygen studies in the COPD group, PCO2 increased and pH fell by the end of exercise significantly (PCO2 increase, 43.8 ± 1.7 to 48.9 ± 2.3 mm Hg [p = 0.001]; pH decrease, 7.38 ± 0.01 to 7.34 ± 0.01 [p < 0.001]). Blood lactate levels did not differ at rest between groups or between inhalations. Following exercise onset, the lactate level remained at resting levels for the first 2 min of exercise and then mildly and gradually rose before reaching a steady state 6 to 8 min into the exercise period. The end-exercise lactate levels did not differ significantly between subject groups or inhalations (Fig 4).

Linear regression analysis did not reveal significant correlation between the rest-to-end-exercise change in lactate levels and the VO2 time constant with either inhalation in either group.

**DISCUSSION**

Compared to healthy subjects of similar ages, patients with severe COPD demonstrated slow gas exchange and cardiorespiratory response dynamics following the onset of moderate constant-work rate exercise. The presence of hyperoxia engendered a deceleration of VE and VCO2 kinetics without an acceleration of VO2 and HR kinetics in both groups. The slow VO2 dynamics seen in the COPD patients were not accompanied by large transient changes in arterialized venous lactate concentration. Our observations suggest that the improved exercise tolerance observed in nonhypoxemic COPD patients who breathe supplemental oxygen1 is likely not related to improved peripheral muscle function.

Gas exchange responses following the start of moderate-intensity, constant-work rate exercise are characterized by three temporal phases.27 Phase I lasts about 15 to 20 s and represents the immediate
increase in gas exchange, the majority of which is accounted for by the abrupt increase of pulmonary blood flow at the start of exercise.\textsuperscript{28} Phase II is the slower, approximately exponential increase in the kinetic variables resulting from the increased cellular respiration in the working muscles and the further increase in cardiac output. Phase III is the steady state, starting at 3 to 4 min after the onset of exercise when the work rate is moderate. At work rates associated with sustained levels of lactic acidosis, phase III features a further increase in response, thus yielding a slower overall kinetic response.

The factors determining the speed of \( \dot{V}O_2 \) kinetics remain unclear. While some posit that sluggish oxygen delivery to the muscle can slow \( \dot{V}O_2 \) kinetics, others believe that the determining factors are intrinsic to the muscle (e.g., inadequate capillarity\textsuperscript{12} and suboptimal oxidative enzyme performance\textsuperscript{14,15}). Therefore, the finding of Palange et al\textsuperscript{10} that the speed of \( \dot{V}O_2 \) kinetics can be increased appreciably by modest increases in arterial oxygen content assumes considerable importance. First of all, it implies that increasing the fraction of inspired oxygen improves oxygen delivery to the exercising muscle. This is not necessarily so, as oxygen is a vasoconstrictor in peripheral vascular beds.\textsuperscript{18} In both healthy subjects\textsuperscript{29} and in COPD patients\textsuperscript{30} at a given level of exercise, oxygen breathing results in both a reduced muscle blood flow and an increased oxygen content, resulting in a net blunting or elimination of oxygen delivery increase. This possibility is given credence by a report of Simon et al,\textsuperscript{31} who studied patients similar to those studied here, in which femoral vein catheterization allowed the direct measurement of oxygen delivery. During moderate-intensity exercise, oxygen delivery to the leg was not higher when the inhaled oxygen concentration was increased. Second, even if oxygen can be delivered to the muscle at a more rapid rate, the muscle may be unable to utilize it at an accelerated rate.\textsuperscript{32–34} In contrast, endurance exercise training, an intervention that alters muscle structure and biochemistry, has been clearly shown to speed \( \dot{V}O_2 \) kinetics following the onset of moderate exercise in both healthy subjects and COPD patients.\textsuperscript{5,35}

We cannot with certainty explain the difference between our results and those of Palange et al\textsuperscript{10} who found that supplemental oxygen substantially increased the speed of \( \dot{V}O_2 \) kinetics. They employed a mixing-chamber system to evaluate kinetics and observed only a single exercise transition for each inhalation. Furthermore, since the end-exercise oxygen saturation was not stated and the lactate level was not measured, it is conceivable that either exercise-induced desaturation while breathing air was marked or that the work rate was considerably above the LAT, although these were not the authors' intention. An additional possibility, the one that we favor, is that a technical difficulty with measuring \( \dot{V}O_2 \) in the presence of elevated inhaled oxygen could have resulted in a falsely increased speed of \( \dot{V}O_2 \) kinetics. When oxygen breathing commences, the wash-in of oxygen into the lung and body oxygen stores occurs rapidly (i.e., within several minutes) in subjects with normal lungs. However, the lung of the COPD patient may contain poorly ventilated areas that wash out very slowly, or not at all, during quiet breathing. Taking periodic deep breaths may succeed in equilibrating these areas and, thus, may avoid the sudden washout of these airspaces with low oxygen content. Figure 1 presents an extreme example in which the apparent \( \dot{V}O_2 \) kinetics are much faster when equilibration with the higher oxygen inhalation is not complete.

Although the mechanisms linking muscle hypoxia to lactate production are controversial, in a variety of situations interventions that increase muscle oxygen supply lower lactate levels in the blood. We therefore postulated that improvements in oxidative metabolism leading to more rapid \( \dot{V}O_2 \) kinetics would be associated by an attenuation of the transient increase in lactate in the arterialized venous blood. In fact, as shown in Figure 4, only small increases in lactate level were observed in the COPD patients, and oxygen supplementation resulted in no alteration in lactate levels or time course. Furthermore, in the healthy subjects, despite transitioning to a considerably higher work rate, the lactate time course was nearly identical. These data do not support the contention of Cerretelli et al\textsuperscript{36} that slower \( \dot{V}O_2 \) kinetics are associated with an accentuated transient increase in blood lactate ("early lactate").

Reinforcing the findings of previous studies,\textsuperscript{37,38} we found that the dynamics of \( \dot{V}E \) track closely those of \( \dot{V}CO_2 \) in both experimental conditions in both groups. Both \( \dot{V}CO_2 \) and \( \dot{V}E \) kinetics were considerably slower in the COPD patients than in the healthy subjects. In part, this is related to the slower \( \dot{V}O_2 \) kinetics, but a primary role for sluggish ventilatory response kinetics is likely as well.\textsuperscript{39} In both healthy subjects and COPD patients, oxygen supplementation slowed \( \dot{V}CO_2 \) and \( \dot{V}E \) kinetics. This has been tied to the inhibition of the carotid bodies, delaying the ventilatory response to metabolic transients.\textsuperscript{37} In the case of the hyperoxic transition to moderate-work rate exercise in the COPD patients, the rise in arterialized venous \( PCO_2 \) (Fig 4) would be expected to contribute to the wash-in of the body's \( CO_2 \) stores, with a consequent slowing of \( VCO_2 \) kinetics.

The observation that end-exercise ventilation was lower in the COPD patients when oxygen was respired, but that the lactate level was not lower, sheds light on the mechanism of oxygen's ability to
improve exercise tolerance during constant-work rate exercise. It seems unlikely that either pulmonary vasodilation or higher arterial oxygen content play a predominant role; otherwise we would have observed signs of improved muscle function in these studies. Rather, we may speculate that carotid body inhibition by hyperoxia directly inhibits ventilation, allowing for decreased hyperinflation and the foreseeing of ventilatory muscle fatigue.

REFERENCES