Heliox Improves Oxygen Delivery and Utilization during Dynamic Exercise in Patients with Chronic Obstructive Pulmonary Disease

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Rationale: **Normoxic heliox (mixture of 79% He and 21% O_2) may enhance exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). It remains to be determined whether part of these beneficial effects could be ascribed to increased O_2 delivery (O_2DEL) to locomotor muscles.**

Objectives: **To investigate the effects of heliox on peripheral O_2DEL and utilization during exercise in moderate to severe COPD.**

Methods: **Twelve mildly hypoxic or nonhypoxemic men (FEV_1 = 45.0 ± 13.0% predicted) underwent constant-work rate tests (70–80% peak) to the limit of tolerance while receiving heliox or room air. Near-infrared spectroscopy determined changes (Δ) in leg muscle deoxygenation (deoxyhemoglobin concentration [HHb], an index of fractional O_2 extraction), and surface electromyography estimated muscle fiber recruitment (n = 5). $\dot{Q}$ and Sp_{O_2} were monitored by impedance cardiography and pulse oximetry, respectively.**

Measurements and Main Results: **Heliox significantly decreased dynamic hyperinflation and increased exercise tolerance compared with room air (640 ± 95 s vs. 371 ± 100 s; $P < 0.01$). Heliox also accelerated on-exercise dynamics of $\dot{Q}$, which were accompanied by faster O_2 uptake kinetics and slower Δ[HHb] responses ($P < 0.05$). During steady-state exercise, Sp_{O_2}-corrected Δ[HHb] values decreased with heliox despite no significant changes in cardiac output. Muscle fiber recruitment and leg effort scores were also diminished ($P < 0.05$). On a multiple regression analysis, reductions in dynamic hyperinflation, dyspnea, and Δ[HHb] were independently related to improvements in exercise tolerance with heliox ($R^2 = 0.91$; $P < 0.01$).**

Conclusions: **Heliox increases lower limb O_2DEL and utilization during dynamic exercise in patients with moderate to severe COPD. These effects enhance exercise tolerance in this patient population.**

Keywords: chronic obstructive pulmonary disease; helium; exercise tolerance; oxygen consumption; near-infrared spectroscopy

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Expiratory flow limitation and increased operational lung volumes are centrally related to exercise intolerance in patients with chronic obstructive pulmonary disease (COPD). There is renewed interest in determining whether such abnormalities might reduce the convective delivery of oxygen to the exercising muscles and thereby decrease patients' ability to sustain whole-body exercise.

What This Study Adds to the Field

This study demonstrates that a strategy able to ammeliorate expiratory flow limitation and dynamic hyperinflation (heliox) accelerates the dynamics of peripheral muscle utilization of oxygen as a consequence of improved delivery during high-intensity exercise in patients with moderate to severe COPD. Our data provide a scientific rationale for respiratory–mechanical interventions aiming to enhance oxygen delivery to the lower limb muscles during dynamic exercise in this patient population.

There are several putative factors related to decreased exercise capacity in patients with chronic obstructive pulmonary disease (COPD). These range from pulmonary–mechanical abnormalities to impaired muscle bioenergetics (1–3). More recently, much emphasis has been given to the dynamics of oxygen delivery (O_2DEL) to the working muscles as a contributing mechanism (1, 4–6). Reduced O_2DEL to the lower limbs, for instance, could be related to hypoxemia (6), autonomic imbalance (7), blood flow redistribution from peripheral to respiratory muscles (8, 9), derangements in muscle vasodilatation capacity (10), and the negative effects of increased mean intrathoracic pressures and/or excessive pleural pressure swings on central hemodynamic adjustments (11–13). In fact, hyperoxia can speed the kinetics of $\dot{V}O_2$ at the onset of moderate exercise in patients with COPD, suggesting a role for impaired peripheral O_2DEL in limiting the rate of adaptation of aerobic metabolism (4).

Several therapeutic strategies have been used to improve the respiratory–mechanical abnormalities during exercise in patients with COPD with potential beneficial consequences on O_2DEL (as reviewed in Reference 14). Heliox (mixture of 79% He and 21% O_2), in particular, combines favorable effects on lung mechanics (e.g., faster lung emptying and reduced flow turbulence) (15), pulmonary gas exchange (16), and central hemodynamics (17). Recent data demonstrate that heliox reduced leg discomfort during submaximal exercise in patients with COPD, a finding that might be related to enhanced lower limb O_2DEL (18). In this context, we hypothesized that part of the beneficial effects of heliox on exercise tolerance in patients with COPD could be ascribed to increased O_2DEL to the working muscles with consequent improvement in peripheral O_2 utilization. Confirmation of this hypothesis would not only shed new light on the pathophysiologic mechanisms of exercise intolerance in COPD (1–3) but would also

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provide a sounder rationale for respiratory–mechanical interventions aiming to enhance O_2DEL to the appendicular muscles, and thereby exercise tolerance.

This study investigated the effects of heliox on key determinants of peripheral O_2DEL and utilization during high-intensity, constant work rate exercise in patients with moderate to severe COPD. To gain broad mechanistic insights, we performed an integrative analysis considering the dynamic and steady-state exercise responses.

METHODS

See the online supplement for a more detailed version of these methods.

Subjects

Twelve mildly hypoxemic or nonhypoxemic (resting $Pa_{O_2} > 60$ mm Hg) male subjects with moderate to severe, stable COPD ($FEV_1/FVC < 0.7$; postbronchodilator $FEV_1 < 60\%$ predicted) (19) volunteered to participate in the study. Subjects were free of severe pulmonary hypertension, left ventricular dysfunction, and musculoskeletal abnormalities. 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, Brazil.

Study Protocol

The study was a randomized crossover investigation that involved three visits to the laboratory. After determination of the gas exchange threshold (GET) and peak $\dot{V}O_2$ on a maximal incremental cycle exercise test, the subjects performed, on different days, two constant work rate exercise test to the limit of tolerance (Tlim) at the VO_{2GET} plus 60% of the peak $\dot{V}O_2$-VO_{2GET} difference or 70 to 80% peak work rate if the GET had not been identified. During these tests, the subjects were assigned to breath normoxic heliox or room air from a Douglas bag connected to the inspiratory port of a nonrebreathing, two-way valve.

Measurements

Pulmonary function tests. Spirometry, lung diffusing capacity, and static lung volumes by body plethysmography were measured at baseline. Recorded values were compared with those predicted for the adult Brazilian population (20, 21). Arterial partial pressure for O_2 and CO_2 were determined in standard anaerobic conditions.

Exercise tests. Standard metabolic and ventilatory responses were measured breath-by-breath using a calibrated, computer-based system (CardiO$_2$ System; Medical Graphics, St. Paul, MN). The rate of power increments during the ramp exercise test was individually chosen (range, 5–15 W/min) to provide a test duration between 8 to 10 minutes. Peak $\dot{V}O_2$ was the highest value at symptom limitation and compared with Brazilian standards (22). Assuming that TLC remains constant during exercise, serial inspiratory capacity maneuvers were performed to estimate end-expiratory lung volume (EELV) (23). Before the constant work rate tests, the flow sensor and the gas analyzers were calibrated with the experimental gas mixture, and a spirometric test was performed.

Skeletal muscle oxygenation. Skeletal muscle oxygenation profiles of the left vastus lateralis were evaluated with a commercially available near-infrared spectroscopy system (NIRO 200; Hamamatsu Photonics KK, Hamamatsu, Japan). The deoxyhemoglobin concentration ([HHb])/myoglobin (Mb) signal (μM/cm) during exercise has been considered a proxy of fractional O_2 extraction in the microcirculation, reflecting the balance between O_2DEL and utilization (24, 25):

$$O_2\text{DEL} \cong O_2 \text{ utilization } (\dot{V}O_2) \,/\, \text{fractional } O_2 \text{ extraction } (\Delta[\text{HHb}])$$

(i.e., at a given level of O_2 utilization, O_2DEL and fractional O_2 extraction are expected to be inversely related). Δ[HHb] values were expressed as percentage of the maximal value obtained by arterial femoral occlusion with a cuff pressure of 250 mm Hg and are corrected for changes in Sp_{O_2}. Additional details are described in the online supplement.

Central hemodynamics. $\dot{Q}$ and stroke volume (SV) were measured throughout the constant work rate test using impedance cardiography (PhysioFlow PF-05; Manatec Biomedical, Petit-Ebersviller, France) (26). This methodology is different from previously used impedance systems because its algorithm does not require basal thoracic impedance measurement or the estimation of blood resistivity and because the position of the electrodes is not critical for the accuracy of the measurements. Additional information on response characteristics and system validation is given in the online supplement.

Electromyography. A four-channel surface electromyography system (Miotool; Miotec Equipamentos Biomedicos Ltda, Porto Alegre, Brazil) was used to measure the muscle activity from the left vastus lateralis muscle (27). Root mean square values normalized by a previously obtained maximal voluntary contraction were calculated by a mathematical routine using Matlab 7.1 software (Math Works Inc., Natick, MA).

Kinetics Analysis

The breath-by-breath $\dot{V}O_2$, Sp_{O_2}-corrected Δ[HHb], and hemodynamic ($\dot{Q}$, SV, and heart rate [HR]) data were interpolated each second (SigmaPlot 10.0; Systat Software Inc., San Jose, CA). After checking that a slow component was not discernible in the first 180 seconds of exercise, the data were fitted by the following monoexponential equation (28):

$$[Y]_{(t)} = [Y]_{(b)} + Ap(1 - e^{-(t-TDp)/\tau p})$$

where *b* and *p* refer to baseline unloaded cycling and primary component, respectively, and A, TD, and τ are the amplitude, time delay, and time constant of the exponential response, respectively. Therefore, $\tau\dot{V}O_2$ represents the time course of the primary component (i.e., it is an estimate of the muscle $\dot{V}O_2$ kinetics) (29). The overall kinetics of Δ[HHb] (approximate time to reach 63% of the response after the onset of exercise) were determined by the mean response time (MRT = τ + TD). The ratio $\tau\dot{V}O_2$/MRTΔ[HHb] was used as a qualitative index of microvascular O_2DEL kinetics, with higher values indicating slower O_2DEL

TABLE 1. RESTING CHARACTERISTICS AND RESPONSES TO INCREMENTAL EXERCISE (N = 12)

Variables	Values*
Demographic/anthropometric	
Age, years	62.0 ± 5.0
Body mass index, kg/m^2	24.5 ± 5.3
Pulmonary function	
FEV_1, % predicted	45.0 ± 13.0
FVC, % predicted	85.0 ± 10.0
TLC, % predicted	120.0 ± 3.0
RV, % predicted	165.0 ± 45.0
IC, % predicted	74.0 ± 18.0
D_{LCO}, % predicted	45.0 ± 12.0
Pa_{O_2}, mm Hg	72 ± 7
Sa_{O_2}, %	94 ± 2
Pa_{CO_2}, mm Hg	38 ± 4
Incremental exercise	
Power, W	83 ± 23
$\dot{V}O_2$, ml/minute	1,106 ± 256
VO_{2GET}, ml/minute	706 ± 109
$\dot{V}_E$, L/min	40.2 ± 10.2
$\dot{V}_E$/MVV	0.90 ± 0.23
HR, beats/minute	132 ± 26
Sp_{O_2}, %	92 ± 4
Borg dyspnea scores	7 (3–9)
Borg leg effort scores	7 (0–10)

Definition of abbreviations: D_{LCO} = lung diffusing capacity for carbon monoxide; GET = gas exchange threshold; HR = heart rate, IC = inspiratory capacity; MVV = maximal voluntary ventilation; RV = residual volume; Sp_{O_2} = oxygen saturation by pulse oximetry.

* Values are means ± SD with the exception of symptoms (median and range).

TABLE 2. EFFECTS OF HELIOX ON SELECTED RESTING SPIROMETRIC VARIABLES (N = 12)

Variables	Room Air	Heliox
FEV_1, L	1.23 ± 0.44*	1.43 ± 0.55†
FVC, L	2.65 ± 0.73	2.78 ± 0.88†
FEV_1/FVC	0.47 ± 0.10	0.52 ± 0.11
PEF, L/s	3.54 ± 1.06	4.62 ± 1.53†
$FEF_{25-75\%}$, L/s	0.85 ± 0.47	1.24 ± 0.51†
$FEF_{25-75\%}$/FVC, L/s/L	0.32 ± 0.15	0.45 ± 0.18†
IC, L	1.85 ± 0.33	2.17 ± 0.43†

Definition of abbreviations: $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of FVC; IC = inspiratory capacity.

* Values are means ± SD.

† $P < 0.05$.

(30) (i.e., for a given rate of change in O_2 utilization [$\tau\dot{V}O_2$], the dynamics of O_2DEL and fractional O_2 extraction (Δ[HHb]) are expected to be inversely related). Additional information on the kinetic analysis, including data repeatability, is given in the online supplement.

Statistical Analysis

The SPSS version 15.0 statistical software was used for data analysis (SPSS, Chicago, IL). To contrast within-subject exercise responses, paired *t* or Wilcoxon tests were used as appropriate. A one-way, repeated-measures ANOVA was used to compare the physiological variables at quartiles of isotime (i.e., the shortest Tlim between the two interventions on a given subject). Pearson's product moment correlation was used to assess the level of association between continuous variables. The strongest significant contributors were selected for a stepwise backward multiple regression analysis. The level of statistical significance was set at $P < 0.05$ for all tests.

RESULTS

Subject Characteristics and Maximal Exercise Capacity

As expected from the inclusion criteria, patients had moderate to severe airflow obstruction with increased static lung volumes, moderate reductions in D_{LCO}, and normal or slightly abnormal arterial blood gases at rest (Table 1). According to the scheme proposed by the Global Initiative for Obstructive Lung Disease, six patients were stage II, with the remaining subjects being considered as stage III patients (19). All subjects showed reduced maximal exercise capacity (peak $\dot{V}O_2$ below the lower limit of normality) (Table 1) (22). The GET was reliably identified in 10 patients. Pulmonary-ventilatory limitation, at least as suggested by increased peak $\dot{V}E$/MVV ratio (>0.8), was found in all subjects. Only three patients had mild exercise-related oxyhemoglobin desaturation (peak Sp_{O_2} ranging from 92 to 86%). Breathlessness and leg effort were similarly described as the exercise-limiting symptoms (Table 1).

Effects of Heliox on Spirometric Variables

Heliox breathing was associated with significant increases in FEV_1, FVC, and expiratory flows (Table 2; $P < 0.01$). As a likely consequence of the enlarged maximal flow-volume envelope, tidal flow-volume loops no longer reached the maximal envelope in 5 of 12 patients (data not shown). Heliox also reduced resting lung hyperinflation, as estimated by IC maneuvers ($P < 0.05$; Table 2).

Estimated O_2DEL and Utilization Dynamics at the On-Exercise Transient

We found that the dynamics of the primary component of $\dot{V}O_2$ were approximately 27% faster with heliox compared with room air (Table 3). These beneficial effects were accompanied by an even larger speeding effect on QT kinetics (~39%) due to more rapid HR (~40%) and SV (~24%) responses ($P < 0.05$; Table 3). There were no significant effects of heliox on the time delay for Δ[HHb] increase; conversely, τΔ[HHb] was approximately 44% slower with heliox (Figure 1; Table 3). Consequently, MRTΔ[HHb] was significantly increased with heliox compared with room air, indicating that the fractional O_2 extraction adapted at a slower rate (21.4 ± 2.2 s vs. 18.2 ± 2.9 s, respectively; $P < 0.05$). Consistent with these data, the $\tau\dot{V}O_2$/MRTΔ[HHb] ratio was lower with heliox, suggesting faster kinetics of O_2DEL (4.01 ± 0.94 vs. 2.71 ± 0.89, respectively; $P < 0.01$) (30). Changes in $\tau\dot{V}O_2$/MRTΔ[HHb] with heliox were significantly related to variations on MRT-$\dot{Q}$ ($P < 0.05$) (Figure 2).

Exercise Tolerance and Steady-State Responses

Mean data analysis revealed that Tlim was significantly increased with heliox compared with room air (640 ± 95 seconds vs. 371 ± 100 seconds, respectively; $P < 0.001$) (Figure 3). In fact, 11 of 12 patients cycled longer while breathing heliox, and 7 of 12 patients improved by more than 1.75 minutes, a threshold value suggested to represent the minimal clinically important difference for this test format (31). In relative terms, there was a large variability in these positive effects (median improvement [interquartile range], 43.6–[50.3]).

We found consistent decreases in some indexes of metabolic cost with heliox breathing (i.e., lower $\dot{V}O_2$, $\dot{V}CO_2$, and respiratory exchange rate [R] at Tlim and isotime) (Table 4 and Figure 4A for submaximal $\dot{V}O_2$ response). In contrast, patients seemed to hyperventilate during exercise with heliox as suggested by increased $\dot{V}E/\dot{V}CO_2$ with lower PET_{CO_2} values (Figures 4B–4D; Table 4). This pattern of response was associated with increases

TABLE 3. EFFECTS OF NORMOXIC HELIOX ON THE KINETICS OF SELECTED PHYSIOLOGICAL RESPONSES AT THE START OF HIGH-INTENSITY, CONSTANT WORK RATE EXERCISE (N = 12)

	Room Air				Heliox			
Variables	Baseline	Amplitude	TD (*s*)	τ (*s*)	Baseline	Amplitude	TD (*s*)	τ (*s*)
Metabolic								
$\dot{V}O_2$, ml/minute	615 ± 112*	637 ± 174	17.4 ± 8.5	74.2 ± 28.9	566 ± 95	561 ± 190	16.1 ± 6.9	54.0 ± 14.4†
Cardiovascular								
$\dot{Q}$, L/minute	7.4 ± 1.6	6.6 ± 1.8	—	108.8 ± 48.9	7.0 ± 2.2	6.8 ± 1.6		64.0 ± 25.5†
HR, beats/minute	88 ± 10	51 ± 28	—	113.3 ± 40.7	83 ± 16	48 ± 19		67.5 ± 18.3†
SV, ml/minute	83 ± 15	14 ± 5	—	66.1 ± 26.1	80 ± 18	13 ± 8		49.8 ± 22.3†
Muscle oxygenation								
Δ[HHb]	−9 ± 20	209 ± 154	12.4 ± 2.2	6.1 ± 1.5	1 ± 17	215 ± 120	12.1 ± 2.1	8.8 ± 3.8†

Definition of abbreviations: HHb = deoxyhemoglobin; HR = heart rate; $\dot{Q}$ = cardiac output; SV = stroke volume; TD = time delay.

* Values are means ± SD.

† $P < 0.05$ (between-treatment differences for a given parameter).

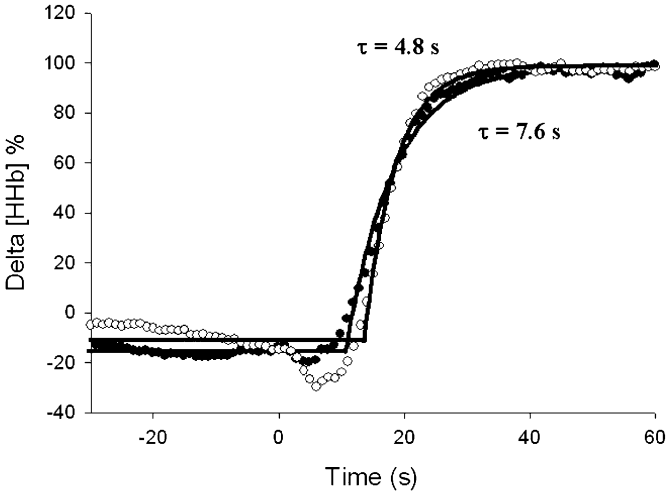

Figure 1. A slower deoxyhemoglobin ([HHb]) response in the vastus lateralis (i.e., higher time constant τ) at the start of high-intensity exercise when normoxic heliox (*solid circles*) was breathed instead of room air (*open circles*) in a representative patient with moderate-to-severe chronic obstructive pulmonary disease. These data suggest a slower adaptation of muscle O_2 extraction as a consequence of improved O_2 delivery.

in f and V_T. Considering that VT and TE-TI varied in opposite directions, mean VT/TI and VT/TE were significantly higher with heliox (*see* Table 4 for MEF). The beneficial effects on the rate of lung emptying were accompanied by lower dynamic hyperinflation, as indicated by reduced EELV values, and reduced dyspnea scores (Table 4). There was also a mild improvement in Sp_{O_2} with heliox (Table 4; Figure 4E). In fact, improvements in Sp_{O_2} greater than 3% at Tlim were found in only 2 of 12 patients. In contrast, the

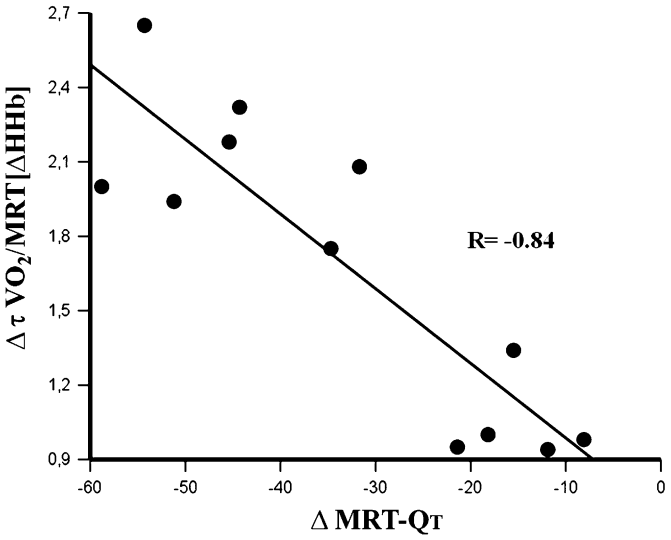

Figure 2. The relationship between changes (Δ = heliox – room air) in a qualitative index of microvascular O_2 delivery ($\tau\dot{V}O_2$/MRT[ΔHHb]) at exercise onset and variations on the dynamics of central cardiovascular adjustments (MRT-Q_T) in patients with moderate to severe chronic obstructive pulmonary disease. Improvements in O_2 delivery (i.e., larger decrements in $\tau\dot{V}O_2$/MRT[ΔHHb]) were related to the beneficial effects of heliox in speeding on-exercise cardiac output (Q_T) kinetics ($P < 0.01$). HHb = deoxyhemoglobin; MRT = mean response time.

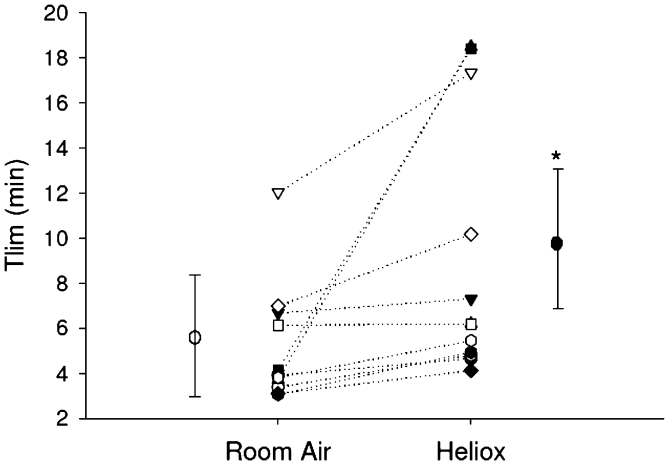

Figure 3. Significant effects of normoxic heliox on time to exercise intolerance (Tlim) in patients with moderate to severe chronic obstructive pulmonary disease (n = 12) ($P < 0.05$).

cardiovascular responses were similar between heliox and room air at this phase of exercise with no significant between-intervention differences in $\dot{Q}$, HR, and SV ($P > 0.05$; Table 4).

Skeletal Muscle Oxygenation, Fiber Recruitment, and Leg Effort Scores

Consistent with the aforementioned positive effects of heliox on O_2DEL at the on-exercise transient (*see* Figure 1 and Table 3), Δ[HHb] was significantly reduced with heliox treatment compared with room air during the steady-state phase of exercise (Figure 4F). Patients also showed lower submaximal root mean square values (Figure 5) and leg effort scores at isotime and exercise cessation while breathing heliox ($P < 0.05$; Table 4).

Correlates of Improvement in Exercise Capacity with Heliox

We found that several pulmonary–mechanical, gas exchange, and perceptual variables correlated with improved exercise capacity (ΔTlim) with heliox, including ΔEELV ($R = 0.70$), ΔVT/TE ($R = 0.67$), ΔVT/TI ($R = 0.65$), ΔSp_{O_2} ($R = 0.56$), and dyspnea scores ($R = 0.64$; $P < 0.05$). In addition, indexes of improved muscle O_2DEL (lower [HHb]) and faster O_2 kinetics (shorter $\tau\dot{V}O_2$) were significantly related to ΔTlim ($R = -0.67$ and $R = -0.61$; $P < 0.05$). On a stepwise multiple regression analysis, decreases in EELV and dyspnea and improvements in VT/TE explained up to 75% of the variance in Tlim ($R^2 = 0.75$; $P < 0.01$). However, reductions in [HHb] during exercise remained an independent predictor of ΔTlim, explaining further 16% of the observed variance ($R^2 = 0.91$; $P < 0.01$).

DISCUSSION

This is the first study to investigate the effects of normoxic heliox on the determinants of O_2DEL and utilization during heavy-intensity exercise in patients with COPD. The main novel findings of the present study are that heliox (*1*) speeded the on-exercise kinetics of $\dot{Q}$, HR, SV, and pulmonary $\dot{V}O_2$; (*2*) slowed the dynamics of [HHb], a noninvasive index of fractional O_2 extraction; and (*3*) decreased [HHb], muscle fiber recruitment, and leg effort scores during the steady-state phase of exercise. As previously shown (15, 18), patients' ability to sustain high-intensity cycling exercise approximately doubled with heliox. We found that the effect of heliox on steady-state [HHb] was independently associated with the changes in exercise tolerance. These data provide original evidence that strategies aimed to reduce the

mechanical burden of breathing in patients with COPD can improve peripheral O_2DEL and utilization during exercise. This should have positive effects on exercise capacity in this patient population.

Mechanical-Ventilatory Effects of Heliox in COPD

In the present study, we found several pieces of evidence that heliox ameliorated the mechanical-ventilatory derangements associated with advanced COPD. Therefore, maximal inspiratory and expiratory flows were significantly improved at rest (*see* Table 2), which helped to increase the $\dot{V}_E$ "ceiling" to exercise (MVV = $FEV_1 \times 40$). Although heliox led to increased $\dot{V}_E$ response to exercise (15, 18, 32), the same proportional fraction of MVV was attained at a later stage of exercise with heliox compared with room air (Table 4). However, as the EELV decreased (Table 4), it is likely that the work of breathing was reduced at a given $\dot{V}_E$/MVV. Reductions in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at higher $\dot{V}_E$ are also consistent with this concept (Table 4). Despite these beneficial effects, changes in Tlim were quite variable (*see* Figure 3), probably depending on the relative position of the performed work rate compared with individual's highest sustainable work rate or "critical power" (i.e., the closer the work rate to critical power, the larger the potential for improvement after any intervention) (33).

Effects of Heliox on the Determinants of O_2DEL and Utilization in COPD

The factors generally considered as limiting the on-exercise kinetics of $\dot{V}_{O_2}$ are the adequacy of O_2DEL during the transient phase and/or intramyocyte "metabolic inertia" (34). In a previous study (30), we reported that the on-exercise $\dot{Q}$ kinetics at high-intensity exercise were $\sim$ 44% slower in patients with COPD compared with age-matched sedentary control subjects; conversely, the dynamics of [HHb] were significantly faster in patients with COPD. Interpretation of the latter as an estimate of muscle microvascular fractional O_2 extraction suggests that the dynamics of O_2DEL were slower in patients with COPD. The ensuing hypothesis that the central cardiovascular responses were important contributing factors to constrain the rate of muscle O_2 utilization (30, 35) is consistent with the present findings showing that heliox speeded the $\dot{Q}$ kinetics and the phase II $\dot{V}_{O_2}$ kinetics concurrently (*see* Table 3). This contention is further supported by the significant association between changes in the kinetics of $\dot{Q}$ with heliox and changes in a qualitative index of microvascular O_2DEL dynamics ($\tau\dot{V}_{O_2}$/MRTΔ[HHb]) (*see* Figure 2). Our interpretation of these findings is that heliox alleviates disturbances in central hemodynamics imposed by the mechanics of breathing in patients with COPD, permitting a faster increase in muscle O_2DEL and thereby slowing the kinetics of fractional O_2 extraction Δ[HHb] and speeding the $\dot{V}_{O_2}$ dynamics.

In the current investigation, the speeding effect of heliox on $\dot{Q}$ dynamics was due to faster HR and SV adjustments to exercise.

TABLE 4. EFFECTS OF HELIOX ON PHYSIOLOGICAL AND PERCEPTUAL RESPONSES DURING HIGH-INTENSITY, CONSTANT-WORK RATE EXERCISE (N = 12)

	Isotime		Tlim	
Variables	Room Air	Heliox	Room Air	Heliox
Metabolic				
$\dot{V}_{O_2}$, ml/minute	1,258 ± 308*	1,112 ± 212†	1,326 ± 266	1,233 ± 262†
$\dot{V}_{CO_2}$, ml/minute	1282 ± 375	1,017 ± 267†	1,368 ± 296	1,112 ± 226†
R	1.01 ± 0.13	0.91 ± 0.15†	1.03 ± 0.10	0.91 ± 0.13†
Ventilatory/gas exchange				
$\dot{V}_E$, L/minute	37.4 ± 8.9	40.3 ± 6.4†	40.2 ± 9.2	44.1 ± 7.4†
$\dot{V}_E$/MVV	0.85 ± 0.12	0.84 ± 0.13	0.90 ± 0.17	0.89 ± 0.15
$\dot{V}_E/\dot{V}_{O_2}$	30 ± 4	36 ± 5†	30 ± 4	36 ± 4†
$\dot{V}_E/\dot{V}_{CO_2}$	30 ± 7	41 ± 12†	30 ± 6	41 ± 9†
f, breaths/minute	30 ± 7	32 ± 9†	30 ± 4	33 ± 4†
V_T, L	1.24 ± 0.28	1.33 ± 0.31†	1.35 ± 0.30	1.45 ± 0.29†
MEF, L/s	1.02 ± 0.28	1.12 ± 0.25†	1.06 ± 0.24	1.17 ± 0.21†
T_I/T_{TOT}	0.44 ± 0.05	0.43 ± 0.03	0.45 ± 0.03	0.44 ± 0.04
EELV, L	4.20 ± 0.70	4.02 ± 0.57†	4.36 ± 0.83	4.12 ± 0.69†
IRV, L	0.51 ± 0.21	0.62 ± 0.19	0.37 ± 0.27	0.47 ± 0.23
$P_{ET_{CO_2}}$, mm Hg	44 ± 10	35 ± 8†	45 ± 10	35 ± 8†
Sp_{O_2}, %	90 ± 4	92 ± 5†	90 ± 4	92 ± 4†
Cardiovascular				
$\dot{Q}$, L/minute	12.3 ± 3.9	12.1 ± 3.4	12.6 ± 3.5	12.2 ± 4.7
HR, bpm	131 ± 23	129 ± 24	131 ± 22	138 ± 23
SV, ml	95 ± 17	93 ± 19	92 ± 16	87 ± 22
Subjective				
Dyspnea scores	8 (6)	5 (10)†	8 (6)	6 (10)†
Leg effort scores	9 (6)	5 (10)†	9 (10)	6 (10)†

Definition of abbreviations: EELV = end-expiratory lung volume; f = breathing frequency; HR = heart rate; IRV = inspiratory reserve volume; MEF = mean expiratory flow; $P_{ET_{CO2}}$ = end-tidal partial pressure of carbon dioxide; $\dot{Q}$ = cardiac output; R = respiratory exchange rate; SV = stroke volume; T_I, inspiratory time; T_{TOT}, total respiratory time.

* Values are means ± SD with the exception of symptoms (median and range).

† $P < 0.05$.

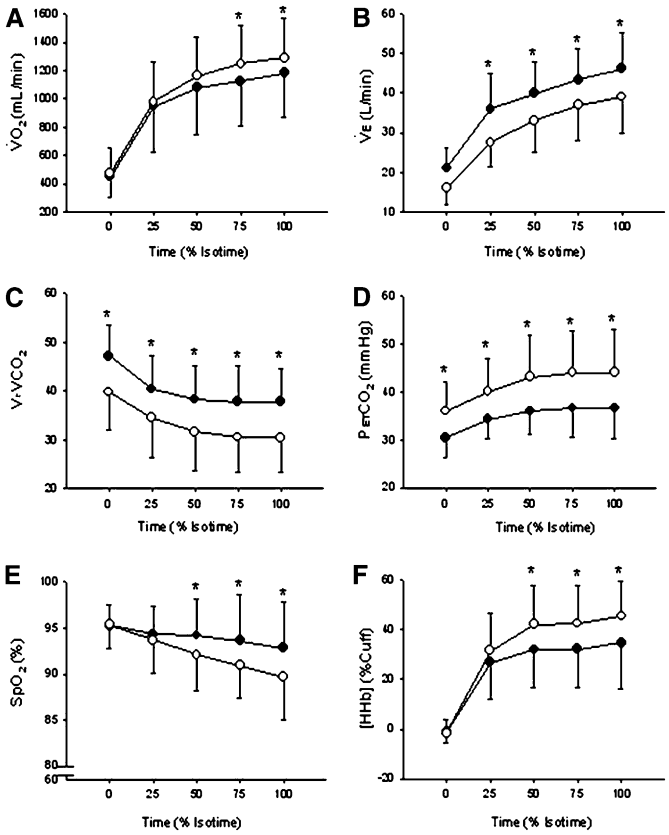

Figure 4. (*A*) Heliox (*solid circles*) was associated with lower overall metabolic cost compared with room air (*open circles*) despite (*B* and *C*) evidence of increased ventilatory responses and (*D*) alveolar hyperventilation during constant work rate exercise. (*E*) Active treatment lessened the exercise-related reductions in oxygen saturation by pulse oximetry (Sp_{O_2}) and (*F*) decreased the Sp_{O_2}-corrected deoxyhemoglobin ([HHb]) values by near-infrared spectroscopy. $P_{ET_{CO_2}}$ = end-tidal partial pressure for carbon dioxide. Isotime is the shortest exercise duration between the two interventions. *$P < 0.05$ (between-treatment effects at a given time point).

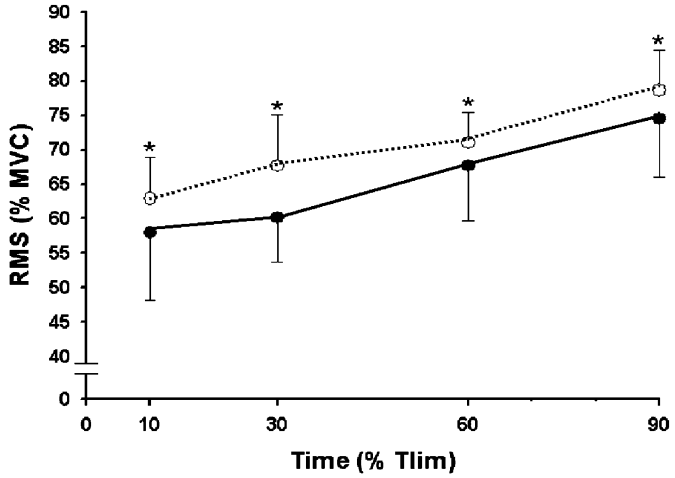

Figure 5. Significant decreases in peripheral muscle fiber activation during constant work rate exercise in response to normoxic heliox (*solid circles*) compared with room air (*open circles*) in patients with chronic obstructive pulmonary disease (n = 5). MVC = maximal voluntary contraction; RMS = root mean square; Tlim = time to exercise intolerance. *$P < 0.05$.

The effects of heliox on airways resistance (18), pulmonary arterial pressure (17), or operating lung volumes (15) may have promoted greater reliance on parasympathetic tone withdrawal for the increase in HR after the onset of exercise. In relation to the SV response, reduction of dynamic hyperinflation with heliox may have allowed tidal breathing to occur on the more favorable, linear portion of the respiratory pressure–volume curve, reducing pleural pressure swings (23). This may have positive effects on left ventricle afterload due to lower transmural pressures (36). In addition, reduction in air trapping and positive pleural pressure during expiration may have improved venous return and decreased the compression of the left ventricle by the overfilled right ventricle (37–39). Moreover, alleviation of dynamic hyperinflation conceivably reduced the expiratory muscle work, decreasing the metabolic (and blood flow) requirements of the abdominal muscles (1).

We found lower values of a noninvasive index of muscle fractional O_2 extraction (Δ[HHb]) with heliox during steady-state exercise (*see* Figure 4F). This has been interpreted as evidence of improved muscle O_2DEL (24, 25). However, the positive effects of heliox on muscle oxygenation were accompanied by decreased muscle fiber recruitment (*see* Figure 4). In this context, we cannot rule out that improvement in O_2DEL with heliox may have selectively decreased the activation of less efficient type II fibers (i.e., with a smaller O_2:ATP ratio), reducing the O_2 cost of work and thereby fractional O_2 extraction (40). This finding might provide further explanation for lower leg effort scores at a given work rate with heliox (Table 4) (18).

Methodological Considerations

A key argument supporting the use of [HHb] as an approximation of O_2 extraction dynamics is the generally similar characteristics of [HHb] response in humans compared with O_2 extraction dynamics measured in skeletal muscles (41) and calculated in computer simulations (25). However, [HHb] and arterial-venous O_2 difference dynamics have not been concomitantly compared. The present findings may not be applicable to lower exercise intensities where the milder ventilatory requirements are likely to decrease the beneficial effects of heliox. It also remains to be determined if hyperoxic heliox would have a synergistic effect in muscle O_2DEL, an effect that could help explaining its better effects compared with normoxic heliox (42).

Conclusions

The present study constitutes the first experimental demonstration that normoxic heliox enhances O_2DEL to and the rate of O_2 utilization ($\dot{V}O_2$ kinetics) by the lower limbs during high-intensity exercise in patients with moderate to severe COPD. These data suggest that the beneficial effects of heliox on peripheral muscle O_2 availability are mechanistically linked to its ergogenic properties in this patient population. Moreover, based on our findings, we propose that therapies aiming to improve the mechanics of breathing can be used to improve lower limb O_2DEL and increase exercise tolerance in patients with COPD.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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