

# Bronchodilators accelerate the dynamics of muscle O<sub>2</sub> delivery and utilisation during exercise in COPD

Danilo C Berton,<sup>1</sup> Priscila B Barbosa,<sup>1</sup> Luciana S Takara,<sup>1</sup> Gaspar R Chiappa,<sup>1</sup> Ana Cristina B Siqueira,<sup>1</sup> Daniela M Bravo,<sup>1</sup> Leonardo F Ferreira,<sup>2</sup> J Alberto Neder<sup>1</sup>

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<sup>1</sup>Pulmonary Function and Clinical Exercise Physiology Unit (SEFICE), Division of Respiratory Diseases, Department of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

<sup>2</sup>Department of Physiology, University of Kentucky, Lexington, Kentucky, USA

## Correspondence to

Professor J A Neder, Pulmonary Function and Clinical Exercise Physiology Unit (SEFICE), Respiratory Division, Department of Medicine, Federal University of São Paulo (UNIFESP), Rua Professor Francisco de Castro 54, Vila Clementino, São Paulo CEP: 04020-050, Brazil; [albneder@pneumo.epm.br](mailto:albneder@pneumo.epm.br)

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## ABSTRACT

**Background** Expiratory flow limitation and lung hyperinflation promote cardiocirculatory perturbations that might impair O<sub>2</sub> delivery to locomotor muscles in patients with chronic obstructive pulmonary disease (COPD). The hypothesis that decreases in lung hyperinflation after the inhalation of bronchodilators would improve skeletal muscle oxygenation during exercise was tested.

**Methods** Twelve non- or mildly hypoxaemic males (forced expiratory volume in 1 s (FEV<sub>1</sub>)=38.5±12.9% predicted; Pao<sub>2</sub>>60 mm Hg) underwent constant work rate cycle ergometer exercise tests (70–80% peak) to the limit of tolerance (Tlim) after inhaled bronchodilators (salbutamol plus ipratropium) or placebo. Muscle (de) oxygenation (~fractional O<sub>2</sub> extraction) was determined in the vastus lateralis by changes (Δ) in the deoxyhaemoglobin/myoglobin signal ([HHb]) from near-infrared spectroscopy, and cardiac output (QT) was monitored by impedance cardiography.

**Results** Bronchodilators reduced lung hyperinflation and increased Tlim compared with placebo (454±131 s vs 321±140 s, respectively; p<0.05). On-exercise kinetics of QT and pulmonary O<sub>2</sub> uptake (V̇O<sub>2</sub>) were accelerated with active treatment; Δ[HHb] dynamics, however, were delayed by ~78% and the signal amplitude diminished by ~21% (p<0.01). Consequently, the ratio between V̇O<sub>2</sub> and Δ[HHb] dynamics decreased, suggesting improved microvascular O<sub>2</sub> delivery ( $\tau \cdot \dot{V}O_2 / MRT \cdot \Delta[HHb] = 4.48 \pm 1.57$  s vs  $2.08 \pm 1.15$  s, p<0.05). Of note, reductions in lung hyperinflation were related to faster QT kinetics and larger decrements in  $\tau \cdot \dot{V}O_2 / MRT \cdot \Delta[HHb]$  (p<0.01).

**Conclusions** Decreases in operating lung volumes after the inhalation of bronchodilators are associated with faster 'central' cardiovascular adjustments to high-intensity exercise with beneficial consequences on muscle oxygenation in patients with moderate to severe COPD.

## INTRODUCTION

Exercise intolerance is a multifactorial construct in patients with chronic obstructive pulmonary disease (COPD).<sup>1–3</sup> In fact, recent studies from our laboratory suggest that expiratory flow limitation and lung hyperinflation are related to sluggish central cardiovascular adjustments at the onset of exercise which might impair the balance between O<sub>2</sub> delivery (QO<sub>2</sub>) and uptake (V̇O<sub>2</sub>) in the exercising muscles of patients with COPD.<sup>4–5</sup> The result, then, is faster and heightened muscle deoxygenation measured by near-infrared spectroscopy (NIRS) in patients compared with age-matched controls.<sup>4</sup> Interestingly, these abnormalities were closely related to slower kinetics of cardiac output

(QT), suggesting an important role for the central cardiovascular adjustments in setting the limits of increase in peripheral QO<sub>2</sub> at the onset of exercise. Further experimental evidence for this contention was obtained in a subsequent study in which a strategy aimed to reduce the resistive work of breathing and dynamic hyperinflation (heliox) simultaneously accelerated the dynamics of QT and QO<sub>2</sub> in patients with moderate to severe COPD.<sup>5</sup> These data prompted the hypothesis that similar findings would be observed in response to the most effective and clinically feasible intervention available to alleviate lung hyperinflation and improve exercise tolerance in these patients—that is, inhaled bronchodilators.<sup>1–6–7</sup>

In the present study, therefore, we aimed to investigate the effects of acute inhalation of a combination of a short-acting β<sub>2</sub>-adrenoceptor agonist (salbutamol sulfate) and a short-acting anticholinergic (ipratropium bromide) on key determinants of QO<sub>2</sub> and V̇O<sub>2</sub> during high-intensity, constant work rate cycling exercise in patients with moderate to severe COPD. Confirmation of the hypothesis that bronchodilators would slow the dynamics and decrease the amplitude of leg muscle deoxygenation would provide novel evidence that amelioration of the mechanical burden of breathing might positively impact upon the provision of O<sub>2</sub> to the working peripheral muscles during exercise in patients with COPD.

## METHODS

### Subjects

Twelve males with moderate to severe, stable COPD (forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) <0.7 and post-bronchodilator FEV<sub>1</sub><60% predicted), and resting Pao<sub>2</sub>>60 mm Hg, volunteered to participate in the study. Patients were recruited from the COPD Outpatients Clinic of the São Paulo Hospital (Brazil), a University-based teaching hospital. Subjects were free of echo Doppler cardiographic evidence of severe pulmonary hypertension and left ventricular dysfunction. No patient has ever been enrolled in a pulmonary rehabilitation programme. All participants signed a written informed consent form. The study protocol was approved by the Institutional Medical Ethics Committee.

### Study protocol

This was a double-blinded, placebo-controlled crossover study. After determination of peak (V̇O<sub>2</sub>) on a maximal incremental cycle ergometer exercise test, subjects were randomly assigned to inhale

salbutamol sulfate 120 µg plus ipratropium bromide 20 µg per actuation, via a metered dose inhaler (MDI; Combivent, Boehringer Ingelheim, Germany) or Combivent placebo via an MDI each on a different day. At these visits, patients performed a total of four transitions from baseline pedalling to 70–80% peak work rate. The initial test was performed to the limit of tolerance (Tlim, min) 20 min after the inhalation of bronchodilators or placebo. Patients rested for 1 h before performing an additional 4 min exercise test. Thus, there were two on-exercise repetitions per day. Data from same-day transitions were averaged to reduce data noise for the kinetic analyses (see details below). Additional details are described in the supplement available online.

## Measurements

### Pulmonary function tests

Spirometry, single-breath lung diffusing capacity, static lung volumes by body plethysmography and arterial blood gases were measured at baseline. Recorded values were compared with those predicted for the adult Brazilian population.<sup>8 9</sup>

### Exercise tests

Standard metabolic and ventilatory responses were measured breath-by-breath using a calibrated, computer-based system (CardiO<sub>2</sub> System, Medical Graphics, St Paul, Minnesota, USA). A period of 3 min unloaded exercise preceded the imposition of the selected work rate. Serial inspiratory capacity (IC, litres) manoeuvres were performed during the test. Assuming that total lung capacity (TLC) remains constant during exercise, IC manoeuvres provide an estimate of end-expiratory lung volume.<sup>10</sup>

### Skeletal muscle oxygenation

Skeletal muscle oxygenation profiles of the left vastus lateralis were evaluated with a commercially available NIRS system (Hamamatsu NIRO 200, Hamamatsu Photonics KK, Japan). The (deoxyhemoglobin (Hb)/myoglobin (Mb) signal ([HHb], µM/cm) during exercise has been considered a proxy of fractional O<sub>2</sub> extraction in the microcirculation, reflecting the balance between O<sub>2</sub> delivery and utilisation<sup>11 12</sup>—that is,  $\Delta[\text{HHb}] \cong \dot{V}\text{O}_2/\text{QO}_2$ . Additional details are described in the supplement online.

### Central haemodynamics

Cardiac output (QT, l/min) and stroke volume (SV, ml) were measured throughout the constant work rate test using impedance cardiography (PhysioFlow PF-0, Manatec Biomedical, Macheren, France).<sup>13</sup> This methodology is different from previously used impedance systems as its algorithm does not require basal thoracic impedance measurement (Z0). Considering, however, the controversy on the accuracy of the system in providing reliable absolute values of SV in patients with COPD,<sup>14 15</sup> exercise haemodynamic data were also expressed as 'Δ' from baseline. Additional information on response characteristics and system validation are detailed in the supplement online.

### Kinetics analysis

The breath-by-breath  $\dot{V}\text{O}_2$ ,  $\Delta[\text{HHb}]$  and haemodynamic (QT, SV and heart rate (HR)) data from same-day exercise bouts were linearly interpolated to provide second-by-second values and, for each individual, the repetitions were time aligned to the start of exercise and ensemble averaged (SigmaPlot 10.0, Systat Software). The kinetic behaviour of haemodynamic data was estimated by calculation of the half-time of response ( $t_{1/2}$ , s). After checking that a slow component was not discernible in the first

180 s of exercise, metabolic and NIRS data were fitted by the following monoexponential equation from the start of exercise to the third minute<sup>16</sup>:

$$[Y]_{(t)} = [Y]_{(b)} + A p \left( 1 - e^{-\frac{(t-TD)p}{\tau p}} \right)$$

where  $b$  and  $p$  refer to baseline unloaded cycling and primary component, respectively;  $A$ ,  $TD$  and  $\tau$  are the amplitude, time delay and time constant of the exponential response. For  $\dot{V}\text{O}_2$  analysis we deleted the data relative to the first 20 s after exercise onset—that is, the cardiodynamic phase. Therefore,  $\tau\dot{V}\text{O}_2$  represents the time course of the primary component—an estimate of the muscle  $\dot{V}\text{O}_2$  kinetics.<sup>17</sup> The overall kinetics of [HHb] were determined by the mean response time ( $\text{MRT} = \tau + TD$ ). The ratio  $\tau\dot{V}\text{O}_2/\text{MRT} - [\text{HHb}]$  was used as a semiquantitative index of microvascular  $\text{QO}_2$  kinetics, with higher values indicating slower  $\text{QO}_2$ .<sup>4 5</sup> Based on our experience with NIRS in patients with COPD,<sup>4 5 18</sup> and previous findings with other disease populations,<sup>19</sup> we systematically examined whether there was an 'overshoot' in  $\Delta[\text{HHb}]$  after the initial fast response (see the Results section). In the case of a discernible 'overshoot' in the two interventions, we used the area under the 'overshoot' as an additional index of impaired microvascular  $\text{QO}_2$ .<sup>12</sup> Additional information on kinetic analyses are detailed in the supplement online.

### Statistical analysis

Statistical analysis was performed using SPSS 15.0. We planned to evaluate 12 patients based on our previous results in a similar transversal and crossover study with heliox in patients with COPD.<sup>5</sup> Paired  $t$  test was used to contrast within-subject exercise responses with the exception of symptom scores (Wilcoxon signed-rank test). A one-way repeated measures analysis of variance (ANOVA) was used to compare  $\Delta[\text{HHb}]$  at quartiles of isotime—that is, the shortest Tlim between the two interventions on a given subject. Pearson product-moment correlation was used to assess the level of association between continuous variables. The level of statistical significance was set at  $p < 0.05$  for all tests.

## RESULTS

### Subject characteristics and maximum exercise capacity

On average, patients had severe airflow obstruction and lung diffusing capacity for carbon monoxide (DL<sub>CO</sub>) impairment with increased static lung volumes and normal arterial blood gases at rest (table 1). All patients showed reduced maximal exercise capacity (peak  $\dot{V}\text{O}_2 < 83\%$  predicted) (table 1)<sup>20</sup> with increased peak VE/MVV ratio ( $> 0.8$ ). Although dyspnoea was the main limiting symptom in 8/12 patients, Borg scores for leg effort did not differ more than 2 units from the Borg dyspnoea ratings in these patients.

### Effects of bronchodilators on pulmonary function and exercise tolerance

Treatment with bronchodilators increased FEV<sub>1</sub> and IC compared with placebo ( $1.30 \pm 0.50$  litres vs  $1.17 \pm 0.56$  litres and  $2.28 \pm 0.83$  litres vs  $1.89 \pm 0.73$  litres, respectively;  $p < 0.001$  for both comparisons). The criteria for a 'positive' bronchodilator response (FEV<sub>1</sub> change  $\geq 12\%$  and 200 ml)<sup>21</sup> were obtained in 7/12 patients, with FEV<sub>1</sub> increases being closely related to changes in FVC.

The subjects exercised at  $53 \pm 10$  W. Exercise tolerance (Tlim) was improved after treatment with bronchodilators ( $321 \pm 140$  s vs  $454 \pm 131$  s, for placebo and bronchodilators, respectively;

**Table 1** Resting characteristics and responses to incremental exercise (n=12)

Variables	Values
Demography/anthropometric	
Age (years)	65.3±6.5
Body mass index (kg/m <sup>2</sup> )	23.4±4.0
Pulmonary function	
FEV <sub>1</sub> , % predicted	38.5±12.9
FVC, % predicted	80.1±9.7
TLC, % predicted	125.4±5.8
RV, % predicted	192.1±35.6
IC, % predicted	70.1±15.9
DL <sub>CO</sub> , % predicted	43.4±14.2
Pao <sub>2</sub> mm Hg	70±8
Sao <sub>2</sub> , %	94±4
PaCo <sub>2</sub> mm Hg	39±5
Peak exercise	
Power W	72±19
Vo <sub>2</sub> ml/min	1215±185
Vo <sub>2</sub> , % predicted	58.7±15.1
VE l/min	40.8±14.0
VE/MVV	0.87±0.18
HR beats/min	135±24
Borg dyspnoea scores	8 (6–10)
Borg leg effort scores	7 (5–9)

Values are means±SD.

DL<sub>CO</sub>, lung diffusing capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; MVV, maximal voluntary ventilation; Pa, arterial partial pressure; RV, residual volume; Sa, arterial saturation; TLC, total lung capacity; Vco<sub>2</sub>, carbon dioxide output; VE, minute ventilation; Vo<sub>2</sub>, oxygen uptake.

p=0.01). Increases in pre-exercise IC were significantly related to  $\Delta$  (bronchodilators–placebo) TLim ( $r=0.72$  (95% CI 0.31 to 0.91);  $p=0.04$ ). As previously described,<sup>13</sup> increases in IC during exercise were accompanied by larger tidal and inspiratory reserve volumes and lower dyspnoea scores at isotime (table 2). In contrast, there were no significant effects of bronchodilators on mean SpO<sub>2</sub> values (table 2), and improvements in SpO<sub>2</sub> >3% at isotime were found in only 3/12 patients. Similarly, there were no significant between-interventions differences in the cardiovascular responses at the individual isotime (table 2).

### Kinetics response to exercise

Treatment with bronchodilators accelerated the central haemodynamic responses at the onset of exercise ( $t_{1/2}QT=75.9\pm10.3$  s vs  $58.9\pm18.9$  s ( $p=0.02$ ),  $t_{1/2}HR=78.2\pm13.0$  s vs  $62.5\pm15.5$  s ( $p=0.03$ ),  $t_{1/2}SV=51.0\pm8.1$  s vs  $40.6\pm10.3$  s ( $p=0.02$ ) for placebo and bronchodilators, respectively). In relation to the Vo<sub>2</sub> response, there were no significant differences in baseline (unload exercise) and amplitude comparing bronchodilators and placebo ( $508\pm147$  ml/min vs  $528\pm117$  ml/min ( $p=0.87$ ) and  $554\pm98$  ml/min vs  $532\pm108$  ml/min ( $p=0.90$ )). In contrast, the dynamics of the ‘primary’ component of Vo<sub>2</sub> were significantly faster after bronchodilation (table 3).

Bronchodilators slowed the kinetics of leg muscle deoxygenation compared with placebo (figure 1, table 3), despite no significant effects on baseline  $\Delta$ [HHb] ( $3\pm15$   $\mu$ M/cm vs  $2\pm13$   $\mu$ M/cm;  $p=0.83$ ). Therefore,  $\tau\Delta$ [HHb] post-bronchodilators was, on average, twofold the postplacebo value (table 3). Consequently, the  $\tau\text{-Vo}_2/\text{MRT-}\Delta$ [HHb] ratio, an index

**Table 2** Isotime values of selected physiological and perceptual responses during high-intensity, constant work rate exercise after placebo or bronchodilators (n=12)

Variables	Placebo	Bronchodilators	P Value
Metabolic			
Vo <sub>2</sub> (ml/min)			
Exercise	1107±300	1180±355	0.94
$\Delta$ exercise–rest	808±128	835±141	0.86
VCO <sub>2</sub> (ml/min)	1110±293	1221±335	0.88
RER	1.00±0.07	1.04±0.08	0.90
Ventilatory/gas exchange			
VE (l/min)	37.6±15.8	41.3±17.4	0.02
VE/MVV	0.87±0.10	0.88±0.11	0.90
f (respirations/min)	31±4	31±5	0.95
VT (litres)	1.24±0.46	1.34±0.50	0.02
IC (litres)			
Exercise	1.67±0.58	2.02±0.65	0.02
$\Delta$ exercise–rest	−0.29±0.18	−0.25±0.20	0.78
IRV (litres)	0.48±0.17	0.32±0.15	0.01
SpO <sub>2</sub> (%)	91±3	90±2	0.88
Cardiovascular			
QT (l/min)			
Exercise	11.7±3.1	11.6±2.9	0.92
$\Delta$ exercise–rest	4.4±1.0	4.3±0.9	0.87
HR (bpm)			
Exercise	133±22	134±24	0.68
$\Delta$ exercise–rest	54±18	52±14	0.74
SV (ml)			
Exercise	89±18	88±16	0.81
$\Delta$ exercise–rest	28±15	26±19	0.75
Subjective			
Dyspnoea scores	8 (6–10)	6 (4–8)	0.03
Leg effort scores	7 (4–9)	5 (3–8)	0.04

Values are means ± SD, with the exception of subjective variables (median and range). bpm, beats per minute; f, breathing frequency; HR, heart rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; QT, cardiac output; RER, respiratory exchange rate; SpO<sub>2</sub>, oxygen saturation by pulse oximetry; SV, stroke volume; Vco<sub>2</sub>, carbon dioxide output; VE, minute ventilation; Vo<sub>2</sub>, oxygen uptake; VT, tidal volume.

of impaired microvascular QO<sub>2</sub><sup>4 5</sup> decreased after the inhalation of bronchodilators ( $4.48\pm1.57$  s vs  $2.08\pm1.15$  s, for placebo and bronchodilators, respectively;  $p<0.001$ ). There was a close association between reductions in  $t_{1/2}QT$  and lower  $\tau\text{-}\dot{V}O_2/\text{MRT-}\Delta$ [HHb] values after active treatment ( $r=0.88$  (95% CI=0.64 to 0.96);  $p=0.008$ ). Furthermore, the area under the ‘overshoot’ of the  $\Delta$ [HHb] response, a pattern of abnormality associated with impaired microvascular QO<sub>2</sub><sup>12</sup> decreased ( $n=3$ ;  $p=0.04$ ) or disappeared ( $n=4$ ) after bronchodilator treatment compared with placebo.

Interestingly, the decrease in lung hyperinflation (ie, higher IC) was significantly related to faster QT (figure 2A) and Vo<sub>2</sub> kinetics ( $r=-0.73$  (95% CI −0.34 to −0.91);  $p=0.03$ ) but slower rates of muscle deoxygenation ( $\text{MRT-}[\text{HHb}]$ ,  $r=-0.78$  (95% CI −0.40 to −0.92);  $p=0.03$ ). Therefore, patients with larger increases in IC after the inhalation of bronchodilators had greater decrements in  $\tau\text{-}\dot{V}O_2/\text{MRT-}\Delta$ [HHb] (figure 2B).

### Muscle oxygenation and leg effort scores at steady-state exercise

The amplitude of  $\Delta$ [HHb] after the initial ‘fast’ response was significantly reduced with bronchodilators compared with placebo ( $185\pm115$   $\mu$ M/cm vs  $153\pm108$   $\mu$ M/cm;  $p=0.009$ ), remaining lower throughout exercise (figure 3).  $\Delta$ [HHb] at isotime was significantly related to larger postbronchodilator increases in IC ( $r=-0.82$  (95% CI −0.62 to −0.94);  $p=0.01$ ) and

**Table 3** Comparative effects of inhaled placebo vs bronchodilators (BDs) on selected parameters of the kinetics of pulmonary oxygen uptake ( $\dot{V}O_2$ ) and deoxyhaemoglobin ( $\Delta[HHb]$ ) in the vastus lateralis at the onset of high-intensity, constant work rate exercise (n= 12)

	TD (s)			$\tau$ (s)			MRT (s)		
	Placebo	BDs	p Value	Placebo	BDs	p Value	Placebo	BDs	p Value
$\dot{V}O_2$ ml/min	23.2 $\pm$ 7.5	20.3 $\pm$ 7.1	0.67	89.4 $\pm$ 20.1	69.8 $\pm$ 15.4	0.01	106.3 $\pm$ 18.0	84.1 $\pm$ 12.2	0.003
$\Delta[HHb]$ $\mu$ M/cm	10.2 $\pm$ 2.3	10.1 $\pm$ 1.7	0.94	4.9 $\pm$ 1.8	9.1 $\pm$ 3.2	0.001	15.7 $\pm$ 3.0	19.8 $\pm$ 3.2	0.007

Values are means  $\pm$  SD.

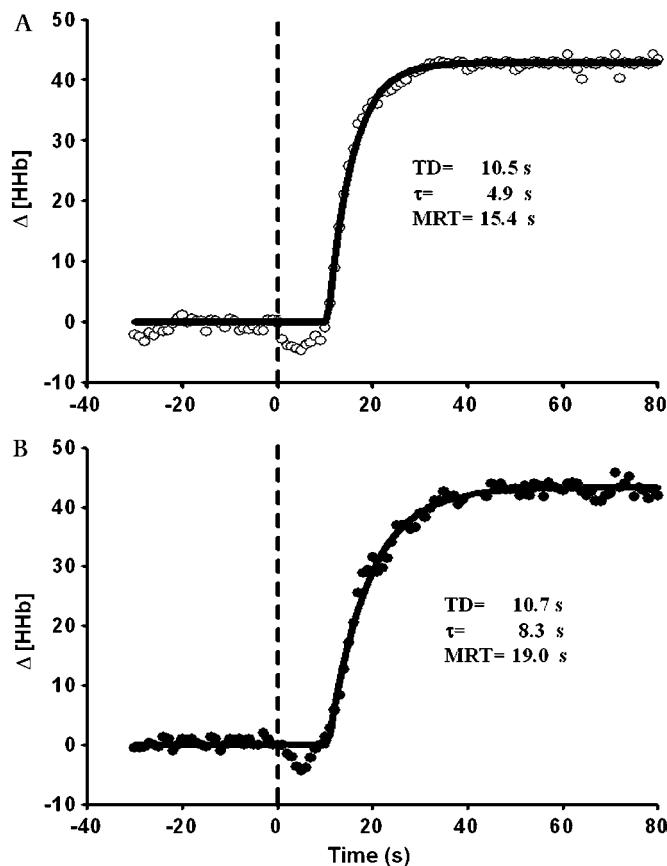
MRT, mean response time; TD, time delay;  $\tau$ , time constant.

improvements in Tlim ( $r=-0.80$  (95% CI=-0.54 to -0.92);  $p=0.01$ ). Leg effort scores at isotime were also lower after active treatment compared with placebo (table 2) and they were marginally related to changes in Tlim ( $r=-0.53$ ;  $p=0.08$ ).

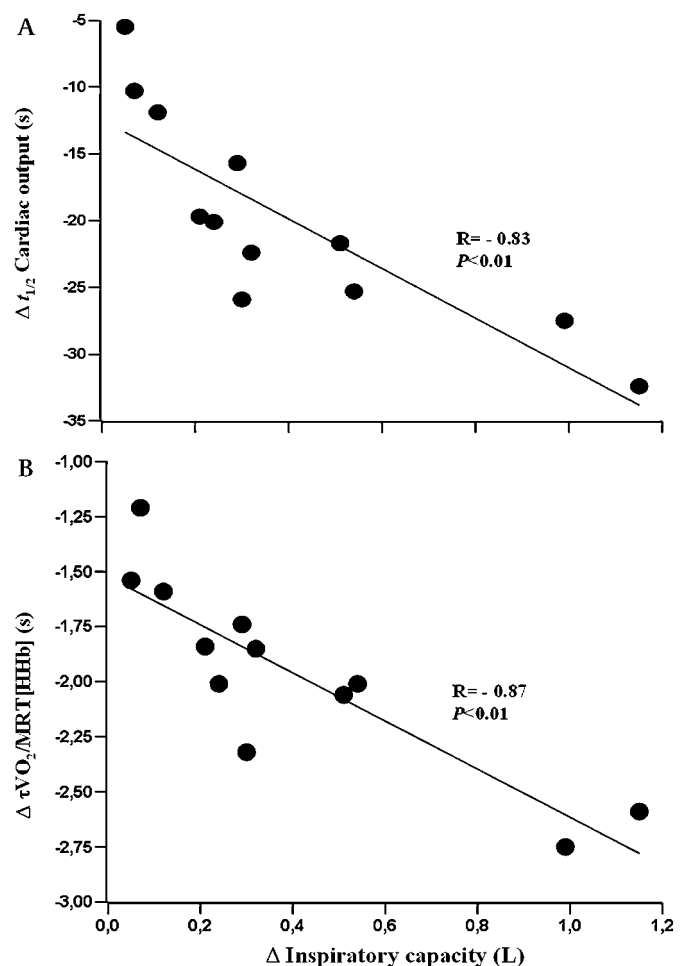
## DISCUSSION

This seems to constitute the first study to investigate the effects of inhaled bronchodilators on the determinants of (estimated) microvascular  $O_2$  delivery ( $QO_2$ ) and utilisation (phase II pulmonary  $\dot{V}O_2$  kinetics) during exercise in patients with COPD. The main novel findings of the present study are that treatment with inhaled bronchodilators to reduce airflow obstruction and lung hyperinflation were associated with: (1) faster on-exercise dynamics of QT and  $\dot{V}O_2$ ; (2) slower kinetics and decreased amplitude of muscle deoxygenation, estimated by  $\Delta[HHb]$ ; and

(3) lower leg effort scores. The relationship between lower operating lung volumes after bronchodilators (ie, larger IC) with faster 'central' haemodynamic adjustments to exercise (QT) and improved muscle oxygenation ( $\tau\dot{V}O_2$ /MRT- $\Delta[HHb]$ ) suggest a mechanistic link between dynamic hyperinflation and impaired  $QO_2$  in these patients. Our data, therefore, provide novel evidence that by alleviating the mechanical burden of breathing in patients with COPD pharmacological bronchodilation promotes an enhancement of  $O_2$  delivery to the working peripheral muscles.

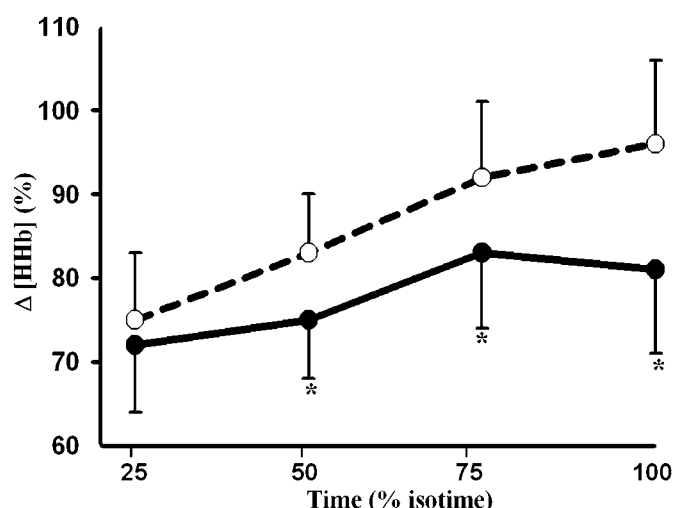


**Figure 1** Comparative effects of inhaled placebo (A) and bronchodilators (B) on changes in deoxyhaemoglobin ( $\Delta[HHb]$ ) by near-infrared spectroscopy in the vastus lateralis in a patient with severe COPD. Note that bronchodilation was associated with slower  $\Delta[HHb]$  adjustments. These data are consistent with improved microvascular  $O_2$  delivery to the peripheral muscles after bronchodilation. TD, time delay;  $\tau$ , time constant; MRT, mean response time.



**Figure 2** Increases in inspiratory capacity (IC) with inhaled bronchodilators ( $\Delta$ =bronchodilator-placebo) were associated with faster cardiac output (QT) kinetics (A) and larger decrements in  $\tau(\dot{V}O_2)$ /MRT- $\Delta[HHb]$  (B). Collectively, these data suggest that improvement in central cardiovascular adjustments after reduction in the operating lung volumes with inhaled bronchodilators (A) led to faster dynamics of microvascular  $O_2$  delivery (B).  $t_{1/2}$ , half-time;  $\tau$ , time constant; MRT, mean response time;  $\dot{V}O_2$ , oxygen uptake;  $[HHb]$ , deoxyhaemoglobin by near-infrared spectroscopy.





**Figure 3** Effects of inhaled bronchodilators (filled symbols) and placebo (open symbols) on skeletal muscle deoxyhaemoglobin ( $\Delta[\text{HHb}]$ , % of maximal value obtained on a previous leg occlusion) in the vastus lateralis at standardised time points during high-intensity exercise. Isotime, the shortest exercise test between the two interventions on a given subject. Values are mean and standard error.

### INTERPRETING THE KINETICS OF MUSCLE OXYGENATION DURING EXERCISE

NIRS is a non-invasive technique that allows continuous measurement of key determinants of peripheral muscle oxygenation during exercise. The time course of  $\Delta[\text{HHb}]$  reflects the local balance between  $\text{QO}_2$  and  $\dot{V}\text{O}_2$  in the area under investigation.<sup>11–12</sup> Previous studies have shown that  $\Delta[\text{HHb}]$  provides a surrogate of fractional  $\text{O}_2$  extraction,<sup>22–23</sup> and its measurement in parallel with (muscle) phase II of the kinetics of pulmonary  $\dot{V}\text{O}_2$  can be used to make useful inferences regarding microvascular  $\text{QO}_2$  via the Fick principle.<sup>4–5, 11–12, 22–23</sup> Therefore, the muscle haemodynamic response at the onset of exercise is characterised by an initial 'phase I' response centrally related to the mechanical effect of muscle contraction (ie, muscle pump) and a slower 'phase II' matched with metabolic demand. Conversely, muscle ( $\dot{V}\text{O}_2$ ) response seems to be well characterised by a single monoexponential function from the start of exercise.<sup>24</sup> Therefore, the resulting response of fractional  $\text{O}_2$  extraction ( $\sim[\text{HHb}]$ ) encompasses an early delay where  $\text{O}_2$  delivery meets (or exceeds) demand (TD) and a rapidly increasing response when the dynamics of capillary flow blood are slower than the rate of change in  $\dot{V}\text{O}_2$ .<sup>11–12</sup> Consequently, the overall  $[\text{HHb}]$  kinetics are expected to be inversely related to the dynamics of  $\text{QO}_2$ .<sup>4–5, 11–12, 22–23</sup>

In some specific circumstances, this pattern of response is further complicated by a transient 'overshoot' in  $\Delta[\text{HHb}]$ ,<sup>25–27</sup> indicating an increase in fractional  $\text{O}_2$  extraction above the steady-state level due to impaired phase II blood flow relative to muscle  $\dot{V}\text{O}_2$ .<sup>12</sup> Consistent with these assumptions, previous studies found an 'overshoot' in  $\Delta[\text{HHb}]$  in patients with type 2 diabetes,<sup>25</sup> chronic heart failure<sup>19</sup> and COPD.<sup>4</sup> The effects of bronchodilators on these complex inter-relationships, however, have not been previously investigated in patients with COPD.

### EFFECTS OF BRONCHODILATORS ON LEG $\text{O}_2$ DELIVERY

The present study provides novel evidence that alleviation of airflow obstruction after pharmacological bronchodilation, with consequent reductions in lung hyperinflation (table 2), resulted

in slower kinetics and lower amplitude of muscle deoxygenation (table 3 and figure 3, respectively). In addition, bronchodilators lessened or eliminated the 'overshoots' in  $\Delta[\text{HHb}]$ , further indicating that muscle oxygenation improved after active treatment. Although the precise mechanism(s) leading to enhanced leg oxygenation could not be determined in this non-invasive study, it is noteworthy that active treatment accelerated the kinetics of the 'central' haemodynamic adjustments to exercise. In this context, a decrease in the operating lung volumes might have been associated with increased reliance of parasympathetic control of HR,<sup>26</sup> an effect that could be related to less airways compression<sup>27</sup> and lower pulmonary arterial pressure.<sup>28</sup> Reduction in air trapping and expiratory positive pleural pressure may have increased venous return, decreased pulmonary vascular resistance and lessened the compression of the left ventricle by the overfilled right ventricle.<sup>29</sup> As there was a close association between faster QT kinetics and reductions in  $\tau(\dot{V}\text{O}_2)/\text{MRT}-\Delta[\text{HHb}]$ , an index of impaired microvascular  $\text{QO}_2$ ,<sup>4–5</sup> it is likely that the slower changes in muscle deoxygenation were driven by quicker 'central' haemodynamic responses at the onset of exercise. Consistent with this notion, Laveneziana and colleagues recently found significant correlations between faster HR dynamics and improved  $\dot{V}\text{O}_2$  kinetics after inhaled bronchodilators in patients with moderate COPD ( $\text{FEV}_1=57\pm 19\%$  predicted).<sup>30</sup>

Other potential mechanisms for the faster on-exercise dynamics of QT and improved muscle oxygenation are related to the pharmacological properties of the bronchodilators. Although the limited available evidence suggests that inhaled bronchodilators have few haemodynamic effects during exercise in patients with COPD,<sup>6–28</sup> their role in modulating skeletal muscle blood flow at the exercise transient in animals is still controversial.<sup>31</sup> Additional studies, therefore, are warranted to address this specific issue in patients with COPD.

Interestingly,  $\Delta[\text{HHb}]$  remained lower during steady-state exercise after the inhalation of bronchodilators (figure 3) despite no significant increases in QT or  $\text{SpO}_2$  (table 2). This finding raises the intriguing hypothesis that alleviation of the respiratory muscle work with bronchodilators may have redirected a fraction of the QT from these muscles back to the appendicular muscles. In fact, we previously reported that respiratory muscle unloading by proportional assisted ventilation increased microvascular  $\text{QO}_2$  at the same QT, suggesting improved perfusion due to blood flow redistribution from respiratory to working peripheral muscles.<sup>18</sup> Further studies are needed to apportion the role of lower operating lung volumes and improved muscle oxygenation in enhancing exercise tolerance in patients with COPD.

### STUDY LIMITATIONS

Constant work rate exercise tests at 70–80% peak have been recognised as the most sensitive testing modality to unravel the functional benefits of bronchodilators.<sup>32</sup> However, our findings may not be relevant to milder exercise intensities where lower ventilatory requirements may decrease, or even abolish, the beneficial effects of bronchodilators on muscle deoxygenation. We also recognise that the use of cycling instead of walking may have contributed to magnify the positive effects of bronchodilation on exercise tolerance, as contractile fatigue<sup>33</sup> and the sense of leg effort<sup>34</sup> are more relevant contributors to decrease exercise capacity in the former modality. It should also be acknowledged that our non-hypercapnic patients with advanced COPD were severely hyperinflated and they presented with substantial reductions in  $\text{DL}_{\text{CO}}$  (table 1)—that is, a disease profile more

compatible with the emphysematous subtype. Consequently, our results should be cautiously extrapolated to other COPD phenotypes. Finally, most of the correlation coefficients had wide confidence intervals, a likely consequence of the small sample size. Therefore, it is advisable that these specific results be confirmed in larger studies.

## CONCLUSIONS

The present study showed that administration of inhaled short-acting bronchodilators to reduce lung hyperinflation slowed the dynamics and reduced the amplitude of muscle deoxygenation during high-intensity cycling exercise in patients with moderate to severe COPD. Considering that these findings were associated with faster on-exercise kinetics of QT and the 'metabolic' phase of pulmonary  $\dot{V}O_2$ , our data are consistent with a speeding and heightening of  $O_2$  delivery to skeletal muscles of patients with COPD treated with inhaled bronchodilators.

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## REFERENCES

1. Aliverti A, Macklem PT. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles. *J Appl Physiol* 2008;**105**:749–51.
2. Debigaré R, Maltais F. The major limitation to exercise performance in COPD is lower limb muscle dysfunction. *J Appl Physiol* 2008;**105**:751–3.
3. O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J Appl Physiol* 2008;**105**:753–755.
4. Chiappa GR, Borghi-Silva A, Ferreira LF, et al. 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* 2008;**104**:1341–50.
5. Chiappa GR, Queiroga F Jr, Meda E, et al. Heliox improves oxygen delivery and utilization during dynamic exercise in patients with COPD. *Am J Respir Crit Care Med* 2009;**179**:1004–10.
6. Saito S, Miyamoto K, Nishimura M, et al. Effects of inhaled bronchodilators on pulmonary hemodynamics at rest and during exercise in patients with COPD. *Chest* 1999;**115**:376–82.
7. Hanania NA, Donohue JF. Pharmacologic interventions in chronic obstructive pulmonary disease: bronchodilators. *Proc Am Thorac Soc* 2007;**4**:526–34.
8. Neder JA, Andreoni S, Castelo-Filho A, et al. Reference values for lung function tests. I. Static volumes. *Braz J Med Biol Res* 1999;**32**:703–17.
9. Neder JA, Andreoni S, Peres C, et al. Reference values for lung function tests. III. Carbon monoxide diffusing capacity (transfer factor). *Braz J Med Biol Res* 1999;**32**:729–37.
10. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**158**:1557–65.
11. Poole DC, Behnke BJ, Padilla DJ. Dynamics of muscle microcirculatory oxygen exchange. *Med Sci Sports Exerc* 2005;**37**:1559–66.
12. Ferreira LF, Townsend DK, Lutjemeier BJ, et al. Muscle capillary blood flow kinetics estimated from pulmonary  $O_2$  uptake and near-infrared spectroscopy. *J Appl Physiol* 2005;**98**:1820–8.
13. Charloux A, Lonsdorfer-Wolf E, Richard R, et al. A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *Eur J Appl Physiol* 2000;**82**:313–20.
14. Bougault V, Lonsdorfer-Wolf E, Charloux A, et al. Does thoracic bioimpedance accurately determines cardiac output in COPD patients during maximal or intermittent exercise? *Chest* 2005;**127**:1122–31.
15. Kemps HM, Thijssen EJ, Schep G, et al. Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients. *J Appl Physiol* 2008;**105**:1822–9.
16. Whipp BJ, Ward SA, Lamarra N, et al. Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 1982;**52**:1506–13.
17. Poole DC, Barstow TJ, McDonough P, et al. Control of oxygen uptake during exercise. *Med Sci Sports Exerc* 2008;**40**:462–74.
18. Borghi-Silva A, Oliveira CC, Carrasqueira C, et al. Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. *Thorax* 2008;**63**:910–15.
19. Sperandio PA, Borghi-Silva A, Barroco A, et al. Microvascular oxygen delivery-to-utilization mismatch at the onset of heavy intensity exercise in optimally-treated patients with CHF. *Am J Physiol Heart Circ Physiol* 2009;**297**:H1720–8.
20. Neder JA, Nery LE, Castelo A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. *Eur Respir J* 1999;**14**:1304–13.
21. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**:948–68.
22. Grassi B, Gladden LB, Samaja M, et al. Faster adjustment of  $O_2$  delivery does not affect  $\dot{V}O_2$  on-kinetics in isolated in situ canine muscle. *J Appl Physiol* 1998;**85**:1394–403.
23. Ferreira LF, Poole DC, Barstow TJ. Muscle blood flow— $O_2$  uptake interaction and their relation to on-exercise dynamic of  $O_2$  exchange. *Respir Physiol Neurobiol* 2005;**147**:91–103.
24. Saltin B. Exercise hyperaemia: magnitude and aspects on regulation in humans. *J Physiol* 2007;**583**:819–23.
25. Bauer TA, Reusch JE, Levi M, et al. Skeletal muscle deoxygenation after the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 diabetes. *Diabetes Care* 2007;**30**:2880–5.
26. Fagreaus L, Linnarsson D. Autonomic origin of heart rate fluctuations at the onset of muscular exercise. *J Appl Physiol* 1976;**40**:679–82.
27. Bleeker ER. Cholinergic and neurogenic mechanisms in obstructive airways disease. *Am J Med* 1986;**81**:93–102.
28. Tobin MJ, Hughes JA, Hutchison DC. Effects of ipratropium bromide and fenoterol aerosols on exercise tolerance. *Eur J Respir Dis* 1984;**65**:441–6.
29. Buda AJ, Pinsky MR, Ingels NB, et al. Effect of intrathoracic pressure on left ventricular performance. *N Engl J Med* 1979;**301**:453–9.
30. Laveneziana P, Palange P, Ora J, et al. Bronchodilator effect on ventilatory, pulmonary gas exchange, and heart rate kinetics during high-intensity exercise in COPD. *Eur J Appl Physiol* 2009;**107**:633–43.
31. Buckwalter JB, Clifford PS. Autonomic control of skeletal muscle blood flow at the onset of exercise. *Am J Physiol Heart Circ Physiol* 1999;**277**:H1872–7.
32. Casaburi R. Factors determining constant work rate exercise tolerance in COPD and their role in dictating the minimal clinically important difference in response to interventions. *COPD* 2005;**2**:131–6.
33. Saey D, Debigaré R, LeBlanc P, et al. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;**15**:425–30.
34. Pepin V, Saey D, Whittom F, et al. Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**172**:1517–22.