

Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD

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ABSTRACT

Background: Respiratory muscle unloading during exercise could improve locomotor muscle oxygenation by increasing oxygen delivery (higher cardiac output and/or arterial oxygen content) in patients with chronic obstructive pulmonary disease (COPD).

Methods: Sixteen non-hypoxaemic men (forced expiratory volume in 1 s 42.2 (13.9)% predicted) undertook, on different days, two constant work rate (70–80% peak) exercise tests receiving proportional assisted ventilation (PAV) or sham ventilation. Relative changes (Δ %) in deoxyhaemoglobin (HHb), oxyhaemoglobin (O_2Hb), tissue oxygenation index (TOI) and total haemoglobin (Hb_{tot}) in the vastus lateralis muscle were measured by near-infrared spectroscopy. In order to estimate oxygen delivery (DO_{2est} , l/min), cardiac output and oxygen saturation (SpO_2) were continuously monitored by impedance cardiography and pulse oximetry, respectively.

Results: Exercise tolerance (Tlim) and oxygen uptake were increased with PAV compared with sham ventilation. In contrast, end-exercise blood lactate/Tlim and leg effort/Tlim ratios were lower with PAV ($p < 0.05$). There were no between-treatment differences in cardiac output and SpO_2 either at submaximal exercise or at Tlim (ie, DO_{2est} remained unchanged with PAV; $p > 0.05$). Leg muscle oxygenation, however, was significantly enhanced with PAV as the exercise-related decrease in $\Delta(O_2Hb)\%$ was lessened and TOI was improved; moreover, $\Delta(Hb_{tot})\%$, an index of local blood volume, was increased compared with sham ventilation ($p < 0.01$).

Conclusions: Respiratory muscle unloading during high-intensity exercise can improve peripheral muscle oxygenation despite unaltered systemic DO_2 in patients with advanced COPD. These findings might indicate that a fraction of the available cardiac output had been redirected from ventilatory to appendicular muscles as a consequence of respiratory muscle unloading.

Pulmonary ventilatory adjustments, especially dynamic hyperinflation and its sensorial consequences, are centrally related to exercise impairment in patients with chronic obstructive pulmonary disease (COPD).¹ More recently, however, much emphasis has also been placed on peripheral muscle abnormalities as adjunct mechanisms to constrain (or even limit) exercise tolerance in this patient population.²

A more fundamental approach to peripheral muscle dysfunction in patient populations, however, should also take into consideration the issue of local energy supply to the locomotor muscles. There are several lines of evidence suggesting that oxygen delivery to the working muscles may be critically impaired during dynamic exercise in patients with

COPD.^{3–6} In this context, it is interesting to note that some interventions known to unload the respiratory muscles—such as pharmacological bronchodilation,⁷ heliox breathing^{3,4} and non-invasive positive pressure ventilation^{8,9}—are associated with lower leg effort scores and/or reduced blood lactate levels. These findings might indicate that such interventions have improved the central haemodynamics to exercise and/or arterial oxygen content (CaO_2) leading to enhanced oxygen delivery to the peripheral muscles. No previous study, however, has looked at the potential benefit of respiratory muscle unloading on peripheral oxygenation in patients with COPD.

The primary objective of this study was to investigate whether locomotor muscle oxygenation during exercise (as measured by near-infrared spectroscopy, NIRS)¹⁰ would be significantly improved by respiratory muscle unloading (via proportional assist ventilation, PAV)¹¹ in patients with moderate to severe COPD. We also investigated whether this potential effect of respiratory muscle unloading would be associated with increased systemic oxygen delivery to the peripheral muscles (ie, higher cardiac output and/or improved CaO_2).

METHODS

Subjects

The study population comprised 16 men with a clinical and functional diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease criteria, presenting with a forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio < 0.7 and post-bronchodilator $FEV_1 < 60\%$ predicted.¹² The patients were referred from the COPD outpatients clinic of our institution. Before entering the study they were required to be clinically stable for at least 3 months and optimised in terms of medical treatment. No patient had used oral steroids in the preceding 6 months. The patients were also required to present with a resting arterial oxygen tension (PaO_2) of > 8 kPa (60 mm Hg) at room air and no evidence of severe pulmonary hypertension (estimated systolic pulmonary arterial pressure < 40 mm Hg) and/or relevant cardiac dysfunction (including ejection fraction $< 60\%$) as assessed by Doppler echocardiography. Patients gave written informed consent and the study protocol was approved by the medical ethics committee of the Federal University of São Paulo/São Paulo Hospital.

Study protocol

After a ramp incremental cardiopulmonary exercise test on a cycle ergometer, the patients performed,

on a separate day, a high-intensity constant work rate (WR) trial test at 70–80% peak WR to individually select the flow and volume assist levels of proportional assisted ventilation (PAV). At subsequent experimental visits the patients undertook, on separate days, two post-bronchodilator constant WR tests at the previously defined WR to the limit of tolerance (Tlim). During these tests they were randomly assigned to receive sham ventilation or the preselected levels of PAV.

Non-invasive positive pressure ventilation

PAV was applied via a tight-fitting partial face mask with pressure levels being delivered by a mechanical ventilator (Evita-4, Draeger Medical, Lübeck, Germany). PAV provides ventilatory assistance in terms of flow assist (cm H₂O/l/s) and volume assist (cm H₂O/l) which can unload the resistive and elastic burdens, respectively.^{11–13} Volume assist was initially set by increasing the level of assist by 2 cm H₂O/l until “run-away” was demonstrated; in this phase, flow assist was maintained at 1 cm H₂O/l/s. Afterwards, flow assist was set by increasing its value by 1 cm H₂O/l/s until “run-away” occurred with volume assist being kept fixed at 2 cm H₂O/l. A fraction (80%) of these values was used initially with flow and volume assist settings adjusted for patient comfort to avoid “run-away” during exercise (see Results section for the actual values used during exercise).

Non-invasive sham ventilation was applied by the same equipment using the minimal inspiratory pressure support (5 cm H₂O of inspiratory pressure support and 2 cm H₂O of positive end-expiratory pressure) to overcome the resistance of the breathing circuit, as informed by the ventilator manufacturer. The patients and the accompanying physician were unaware of the ventilation strategy (PAV or sham) under use; this was accomplished by visually isolating the ventilator and its monitor from them.

Measurements

Pulmonary function

Post-bronchodilator spirometric tests were performed using the CPF System (Medical Graphics Corporation (MGC), St Pauls, Minnesota, USA). Carbon monoxide transfer factor (TLCO) was measured by the modified Krogh technique and the static lung volumes were obtained by body plethysmography (Elite System, MGC). Observed values were compared with Brazilian standards.^{14–15} Arterial oxygen and carbon dioxide tensions (PaO₂ and PaCO₂) were determined in standard anaerobic conditions (mm Hg).

Cardiopulmonary exercise test (CPET)

Symptom-limited cycle ergometric CPET tests were performed using a computer-based exercise system (CardiO₂ System, MGC). The following data were recorded as a mean of 15 s: oxygen uptake ($\dot{V}O_2$, ml/min), minute ventilation ($\dot{V}E$, l/min), respiratory rate (RR, rpm) and tidal volume (VT, litres). Oxyhaemoglobin saturation (SpO₂, %) was determined by pulse oximetry (POX 010-340, Medaid, Torrance, California, USA) with its analogue signal being directed to the cardiopulmonary exercise system. From these data, the arterial oxygen content was estimated as $CaO_{2est} \text{ (ml\%)} = 1.39(\text{Hb}) \times SpO_2$. Subjects were also asked to rate their “shortness of breath” at exercise cessation using a 0–10 Borg category ratio scale.

In the maximum progressive exercise test the rate of power increment was individually selected (usually 5–10 W/min) to provide an exercise duration of 8–12 min. Peak $\dot{V}O_2$ was the

highest value found at exercise cessation: predicted values were those of Neder *et al*¹⁶ for the adult Brazilian population. The constant WR tests were performed at 70–80% of the previously determined peak WR to Tlim (min). Capillary samples were collected from the ear lobe for blood lactate measurements (mEq/l) at exercise cessation (Yellow Springs 2.700 STAT Plus, Yellow Springs Instruments, Ohio, USA).

Skeletal muscle oxygenation

Skeletal muscle oxygenation profiles of the left vastus lateralis muscle were evaluated with a commercially available near-infrared spectroscopy (NIRS) system (Hamamatsu NIRO 200, Hamamatsu Photonics KK, Japan). The theory of NIRS has been described in detail elsewhere.^{10–17} Briefly, one fibreoptic bundle carries the NIR light produced by the laser diodes to the tissue of interest while a second fibreoptic bundle returns the transmitted light from the tissue to a photon detector in the spectrometer. The intensity of incident and transmitted light is recorded continuously and, together with the relevant specific extinction coefficients, used for online estimation and display of the changes from the resting baseline of the concentrations of oxyhaemoglobin ([O₂Hb]), deoxyhaemoglobin ([HHb]) and total haemoglobin ([Hb_{tot}]). The last variable has been used as an index of local blood volume as $[Hb_{tot}] = [O_2Hb] + [HHb]$. From these values an additional index of muscle oxygenation was calculated (tissue oxygenation index (TOI) = $100 \times ([O_2Hb]/[Hb_{tot}])$).^{10–16–17} The values were recorded as a change (Δ) from baseline in units of $\mu\text{M}/\text{cm}$. In order to reduce intrasubject variability and improve intersubject comparability, $\Delta[O_2Hb]$ and $\Delta[HHb]$ values were expressed as the percentage of the maximal value determined on a post-exercise maximal voluntary contraction (MVC) or on early recovery ($\Delta[Hb_{tot}]$).¹⁸ Additional methodological considerations of this technique can be found in the online supplement.

Central haemodynamics

Cardiac output (l/min) and stroke volume (l) were measured non-invasively throughout the constant WR tests using an impedance cardiography device (PhysioFlow PF-05, Manatec Biomedical, France). These data were also used to estimate oxygen delivery ($DO_{2est} = \text{cardiac output} \times CaO_{2est}$, l/min). The PhysioFlow device and its methodology have been thoroughly described elsewhere.¹⁹ Before each exercise test the system was autocalibrated taking into consideration age, stature, body mass and blood pressure values: verification of the correct signal quality was performed by visualising the ECG tracing and its first derivative ($d\text{ECG}/dt$) and the impedance waveform (ΔZ) with its first derivative (dZ/dt).²⁰ Additional methodological considerations of this technique can also be found in the online supplement.

Statistical analysis

SPSS Version 13.0 statistical software was used for data analysis. The results are presented as mean (SD) or median (range) for symptom scores. In order to contrast within-subject exercise responses, paired *t* or Wilcoxon tests were used as appropriate. Time course values during the submaximal exercise tests were expressed as a percentage of isotime, defined as the shorter test between the two experimental conditions in a given subject. Repeated measures analysis of variance (ANOVA) was used to compare the cardiovascular and leg oxygenation variables throughout exercise at quartiles of isotime. The level of statistical significance was set at $p < 0.05$ for all tests.

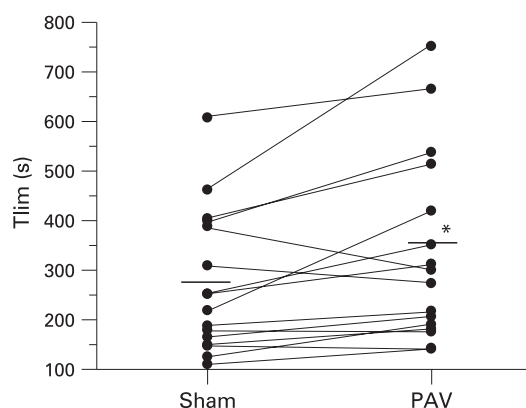


Figure 1 Effects of proportional assisted ventilation (PAV) and sham ventilation on the tolerance to high-intensity constant work rate exercise (Tlim) in 16 patients with moderate to severe chronic obstructive pulmonary disease.

RESULTS

Population characteristics

Patients had moderate to severe airflow obstruction with increased static lung volumes and moderate reductions in TlCO. Seven patients were classified as GOLD stage 2 and the remaining patients were classified as GOLD stages 3–4.¹² All patients presented with reduced maximal exercise capacity (peak $\dot{V}O_2$ below the lower limit of normality).¹⁶ Pulmonary ventilatory limitation, at least as suggested by increased $\dot{V}E_{max}/MVV$ ratio (>0.8), was found in all subjects. Eight patients had mild exercise-related oxyhaemoglobin desaturation (peak SpO_2 ranging from 89% to 86%). Breathlessness and leg effort were similarly described as the exercise limiting symptoms. A detailed description of the main resting and exercise characteristics is given in the online supplement.

Effects of PAV metabolic, ventilatory and perceptual responses

All patients successfully tolerated the two non-invasive ventilation modes during exercise. The actual values for volume

assist and flow assist during PAV were 5.8 (0.9) cm H_2O/l and 3.5 (0.8) cm $H_2O/l/s$, respectively. PAV was associated with a significant increase in exercise tolerance compared with sham ventilation: 337 (189) s vs 273 (142) s ($p = 0.01$). In fact, Tlim improved in 13/16 patients with PAV compared with sham ventilation (fig 1). The reasons for stopping exercise were similar with PAV and sham ventilation (sham ventilation: dyspnoea ($n = 6$), leg fatigue ($n = 8$), both ($n = 2$); PAV: dyspnoea ($n = 8$), leg fatigue ($n = 6$), both ($n = 2$)).

As shown in table 1, $\dot{V}O_2$ was significantly increased at isotime and Tlim with PAV. In contrast, $\dot{V}E$ values were increased only with PAV at Tlim. There were, however, no significant differences in breathing pattern between the two interventions. In addition, leg effort and breathlessness at isotime and corrected for Tlim were significantly reduced with PAV compared with sham ventilation (table 1).

Systemic oxygen delivery and muscle oxygenation

There were no significant effects of PAV on the cardiovascular responses compared with sham. As shown in table 2, stroke volume and cardiac output did not differ between the interventions at isotime and at Tlim. Similar to the maximal exercise test, only eight patients had mild changes in SpO_2 (exercise–rest = -4% to 3%). There was also no significant change in SpO_2 with PAV compared with sham ventilation (table 2): median (range) intrasubject difference in SpO_2 between the two interventions throughout exercise was 0% (-2% to 2%). Consequently, estimated systemic oxygen delivery ($DO_{2est} = \text{cardiac output} \times CaO_{2est}$) remained unchanged with PAV at isotime and Tlim (table 2): median (range) intrasubject difference in DO_{2est} between the two interventions was 0.12 l/min (-0.20 to 0.18).

In relation to muscle oxygenation by NIRS, PAV was associated with lower $\Delta[Hb]$ at 75% isotime, isotime and at Tlim. These changes were accompanied by a significant reduction in the exercise-related decrease in $\Delta[O_2Hb]$ (table 2 and figs 2A and 2B, respectively). Consequently, TOI was improved with PAV at these time points (fig 2C). Moreover, $\Delta[Hb_{tot}]$, an index of local blood volume, was also significantly

Table 1 Effects of proportional assisted ventilation (PAV) and sham ventilation on selected metabolic, ventilatory and subjective responses at isotime (the shortest test between the two experimental conditions in a given subject) and at exercise cessation (Tlim) ($N = 16$)

Variables	At isotime		At Tlim	
	Sham ventilation	PAV	Sham ventilation	PAV
Metabolic				
$\dot{V}O_2$				
Absolute (ml/min)	1110 (334)	1259 (330)*	1126 (335)	1274 (335)*
% peak	98.1 (12.8)	103.6 (13.8)*	99.6 (12.8)	104.4 (16.1)*
Ventilatory				
$\dot{V}E$				
Absolute (l/min)	39.2 (12.6)	41.0 (12.2)	39.8 (12.4)	43.9 (12.7)*
$\dot{V}E/MVV$	0.75 (0.19)	0.78 (0.18)	0.90 (0.29)	1.07 (0.46)
Respiratory rate (bpm)	27 (5)	27 (7)	28 (5)	28 (6)
Tidal volume (l)	1.47 (0.49)	1.56 (0.60)	1.46 (0.49)	1.60 (0.57)
Subjective				
Dyspnoea scores	6 (2–9)	4.5 (3–9)*	6.5 (2–10)	6 (3–10)
Dyspnoea/Tlim (ratings/min)	–	–	1.45 (0.6–1.8)	0.9 (0.2–1.2)*
Leg effort scores	6 (2–9)	4.5 (2–9)*	6.5 (2–10)	6.5 (2–10)
Leg effort/Tlim (ratings/min)	–	–	1.3 (0.7–1.4)	0.95 (0.3–1.2)*

Values are mean (SD) with exception of symptoms (median and range).

* $p < 0.05$ (paired t or Wilcoxon tests for between-group differences at a given time point).

MVV, maximal voluntary ventilation; RER, respiratory exchange ratio; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption.

Table 2 Effects of proportional assisted ventilation (PAV) and sham ventilation on oxygen transport/utilisation variables at isotime (the shortest test between the two experimental conditions in a given subject) and at exercise cessation (Tlim) (N = 16)

Variables	At isotime		At Tlim	
	Sham ventilation	PAV	Sham ventilation	PAV
<i>Cardiovascular/haemodynamics</i>				
Cardiac output				
Absolute (l/min)	12.8 (2.5)	13.0 (3.0)	12.9 (2.5)	13.0 (2.8)
Δ exercise–rest (l/min)	6.5 (2.6)	6.8 (2.8)	6.6 (2.5)	6.9 (2.5)
Stroke volume				
Absolute (ml)	88 (20)	93 (18)	97 (15)	95 (15)
Δ exercise–rest (ml)	18 (13)	20 (14)	22 (12)	22 (15)
Heart rate				
Absolute (bpm)	134 (18)	133 (20)	136 (19)	139 (18)
Δ exercise–rest (bpm)	53 (23)	50 (20)	54 (22)	57 (19)
Oxygen pulse				
Absolute (ml/min/beat)	8.2 (2.0)	8.3 (2.0)	8.2 (1.9)	8.2 (2.0)
<i>Systemic oxygenation</i>				
SpO ₂				
Absolute (%)	90.4 (3.8)	92.3 (1.1)	89.3 (3.6)	90.6 (4.9)
Δ exercise–rest	−4.6 (3.4)	−3.7 (4.4)	−5.7 (3.7)	−5.4 (4.9)
CaO ₂ est (ml%)				
Absolute	18.7 (4.5)	18.2 (3.9)	18.1 (3.6)	18.8 (4.1)
Δ exercise–rest	−2.4 (0.3)	−2.5 (0.6)	−2.3 (0.8)	−2.7 (0.7)
DO ₂ est (l/min)				
Absolute	2.8 (0.4)	2.7 (0.5)	2.5 (0.4)	2.4 (0.3)
Δ exercise–rest	1.9 (0.2)	2.0 (0.3)	1.9 (0.2)	1.8 (0.5)
<i>Leg muscle oxygenation</i>				
Δ[Hb] (% MVC)	88.7 (15.4)	72.9 (16.4)*	90.7 (14.1)	71.8 (15.9)*
Δ[O ₂ Hb] (% MVC)	−85.4 (19.4)	−70.4 (18.8)*	−87.7 (18.7)	−69.3 (19.4)*
Δ[Hb _{tot}] (% recovery)	58.3 (10.9)	74.3 (16.5)*	58.4 (12.3)	77.6 (17.1)*
TOI (%)	35.7 (17.1)	48.7 (18.7)*	34.3 (16.7)	50.2 (19.0)*
<i>Blood lactate</i>				
Absolute (μmol/l)	–	–	3.8 (1.3)	3.9 (1.2)
Lactate/time (μmol/l/min)	–	–	0.99 (0.40)	0.85 (0.35)*

Values are mean (SD).

*p<0.05 (paired *t* test for between-group differences at a given time point).

CaO₂est, estimated arterial oxygen content; DO₂est, estimated oxygen delivery; Hb, reduced haemoglobin; Hb_{tot}, total haemoglobin; MVC, maximum voluntary contraction; O₂Hb, oxyhaemoglobin; SpO₂, oxyhaemoglobin saturation by pulse oximetry; TOI, tissue oxygenation index.

increased with PAV (fig 2D). Consistent with these data, lactate values corrected for Tlim were reduced with PAV compared with sham ventilation (table 2).

DISCUSSION

This study shows that respiratory muscle unloading during exercise (PAV) can improve leg muscle oxygenation (Δ[O₂Hb] and TOI) and local blood volume (Δ[Hb_{tot}]) in patients with moderate to severe COPD. These findings, however, were not related to enhanced systemic DO₂ (cardiac output × CaO₂) to the working muscles. Alternatively, they might indicate that respiratory muscle unloading diminished the blood flow requirements of the respiratory muscles with a consequent redistribution of the available cardiac output from ventilatory to locomotor muscles. From a clinical perspective, our data indicate that strategies aimed at reducing the work of breathing during exercise may present with beneficial effects on energy supply to the peripheral muscles in this patient population.

Methodological considerations

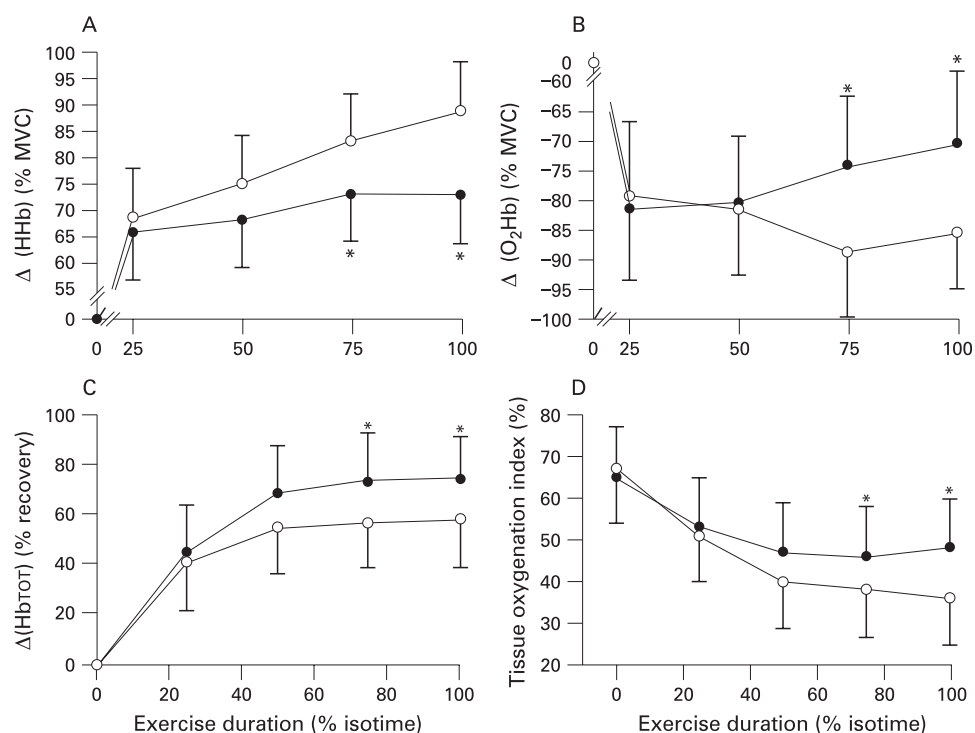
We used PAV in order to unload the respiratory muscles during exercise.^{11–13} Previous studies have found that PAV was superior to other non-invasive strategies in reducing inspiratory muscle

work in patients with COPD. In addition, it was found to be better tolerated by these patients, allowing them to exercise for longer and at significantly higher intensities.^{9–21–22} Unfortunately, however, we were unable to measure the work of breathing directly as small air leaks have profound effects on the levels of assistance by PAV. An oesophageal balloon therefore could not be placed as PAV had to be delivered through a tight-fitting facial mask by the system used in the present study.

We used NIRS to follow the muscle oxygenation patterns continuously during exercise.^{10–17} Although this technique is not able to differentiate between the signal attenuation due to haemoglobin and myoglobin, this confounding factor has been estimated as 10% of the whole haemoglobin signal,¹⁰ a non-critical issue in this within-subject study. In order to improve signal stability and reproducibility we incorporated a number of technical details including the correction of the observed values to maximum values found on post-exercise MVC or recovery. In addition, the changes found with PAV were well above the intrasubject coefficient of variation (CV) for the responses in each subject.

Similar considerations might be applied to cardiac output estimation by impedance cardiography as the system was highly

Figure 2 Comparative analysis of the effects of proportional assisted ventilation (PAV, closed symbols) and sham ventilation (open symbols) on peripheral muscle oxygenation (vastus lateralis muscle) as determined by near-infrared spectroscopy during submaximal exercise (N = 16). PAV lowered the deoxyhaemoglobin concentration ($\Delta[\text{HHb}]\%$) (A) and lessened the exercise-related decrease in oxyhaemoglobin concentrations ($\Delta[\text{O}_2\text{Hb}]\%$) at 75% isotime and at exercise cessation (B). In addition, higher values of total haemoglobin ($\Delta[\text{Hb}_{\text{TOT}}]\%$) were found with active treatment at these time points (C). Consistent with these data, the exercise-related decrease in tissue oxygenation index was lessened with PAV compared with sham ventilation (D). Data are mean (SE). * $p < 0.05$ for between-intervention differences at a given time point (repeated measures one-way ANOVA). MVC, maximum voluntary contraction.



stable during exercise in these patients. However, because of the controversies on the absolute accuracy of this methodology in patient populations,^{23, 24} we first ensured that the system was responsive to small changes in the metabolic demand and the observed values were commensurate with the expected values from the submaximal relationship between the change in cardiac output and the change in $\dot{V}\text{O}_2$ (see online supplement).^{4, 25} In addition, the stroke volume signal remained stable even when dynamic lung hyperinflation was induced in a subgroup of patients (see online supplement).

Energy supply to the locomotor muscles in COPD

It is widely recognised that skeletal muscle oxygenation depends on the dynamic balance between oxygen delivery and utilisation.¹⁰ In the present study PAV was associated with a blunted decrease in exercise $\Delta[\text{O}_2\text{Hb}]\%$ with a consequent improvement in TOI. In addition, $\Delta[\text{Hb}_{\text{TOT}}]\%$, an index of local muscle blood volume,²⁶ was increased with PAV. As a corollary, leg effort- and Tlim-corrected blood lactate levels were diminished with PAV (tables 1 and 2). Moreover, total body $\dot{V}\text{O}_2$ was higher after respiratory muscle unloading (table 1). This finding seems to indicate that peripheral muscle oxygen consumption had been limited by supply before respiratory unloading in these patients, and this more than counterbalanced the potential reductions in respiratory muscle $\dot{V}\text{O}_2$ with PAV. Contrary to our hypothesis, however, these effects were not associated with discernible changes in systemic DO_2est (table 2). Consequently, the enhancement in leg muscle oxygenation during PAV was not secondary to improved intrapulmonary gas exchange and/or enhanced central haemodynamic adjustments to exercise. These findings imply that an alternative mechanism should be sought to explain the improvement in leg oxygen supply with PAV in these patients.

In this context, it is conceivable that peripheral muscle oxygenation has been improved as a consequence of blood flow redistribution from the respiratory to the appendicular muscles.

In other words, respiratory muscle unloading might have reduced the blood flow requirements of the ventilatory muscles with a resultant improvement in appendicular muscle perfusion.⁶ In fact, the increased work of the respiratory muscles during exercise may require up to 50% of the oxygen uptake of the body,^{27, 28} and it is plausible that a fraction of the cardiac output can be diverted from the locomotor muscles to supply the increased energy demands of the ventilatory pump.³⁻⁶ In normal subjects a series of elegant experiments have shown that a respiratory muscle fatigue-induced metaboreflex could increase sympathetic vasoconstrictor outflow, reducing the perfusion of locomotor muscles during exercise (ie, a blood flow “stealing” effect).²⁹⁻³¹ The “stealing” hypothesis is therefore an attractive explanation for our findings: improvement in the intradiaphragmatic milieu with respiratory muscle unloading may have mitigated the noxious metabolic influences leading to a lower leg sympathetic outflow and improved muscle blood flow. The “stealing” hypothesis, however, still awaits additional experimental evidence in these patients, probably by directly measuring the dynamics of diaphragm blood flow during exercise in COPD.³²

Clinical implications

We found that a strategy targeted at reducing the work of breathing and dyspnoea was effective in improving the oxygenation status of the leg muscles. These results therefore emphasise the multifactorial nature of exercise impairment in patients with COPD and provide a rationale for the improvement in leg fatigability with selected interventions which primarily act on the respiratory system. For instance, Peters *et al*⁷ recently reported that the combination of bronchodilators and oxygen was superior to each one in isolation in reducing leg effort scores during exercise in normoxic patients with COPD. Other studies with heliox breathing and non-invasive positive pressure ventilation also found that these interventions were associated with improved DO_2 to the working muscles and

lower submaximal lactate values.^{3 4 8 9} Future clinical trials of the impact of interventions on the mechanical ventilatory responses should look more carefully at the relevance of improved peripheral muscle performance in increasing exercise tolerance in this patient population.

Study limitations

This study has some limitations which are inherent to its non-invasive nature. Although we indirectly estimated local muscle blood volume from the NIRS data, this technique is more sensitive than arterial femoral and whole limb plethysmographic estimates to follow subtle intramuscular changes in perfusion.³³ An intra-arterial catheter was not inserted in our patients and CaO_2 was estimated from continuous SpO_2 readings. We believe that this provided an acceptable surrogate of the true CaO_2 in our non-hypoxaemic patients. We also could not perform inspiratory capacity manoeuvres to estimate the operating lung volumes during exercise with PAV as the sudden increase in ventilation triggers the ventilator to provide additional volume assist. In practice, this is associated with pronounced over-assist, air leaks and acute maladaptation of non-invasive ventilation. Our results should not therefore be extrapolated to more hyperinflated patients than those evaluated in the present study, although the higher oxygen cost of breathing may indicate that the “stealing” phenomenon can also operate in that specific subpopulation. It should also be recognised that it is still unclear whether respiratory muscle unloading would improve peripheral muscle oxygenation during moderate exercise where the ventilatory demands are considerably lower.

In conclusion, respiratory muscle unloading by PAV was associated with increased peripheral muscle oxygenation under stable systemic oxygen delivery during high-intensity constant work rate exercise in patients with moderate to severe COPD. These findings might indicate that a fraction of the available cardiac output had been redirected from ventilatory to appendicular muscles as a consequence of respiratory muscle unloading.

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Competing interests: None.

Ethics approval: Patients gave written informed consent and the study protocol was approved by the medical ethics committee of the Federal University of São Paulo/São Paulo Hospital.

REFERENCES

- Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. *Eur Respir J* 2005;**25**:188–99.
- American Thoracic Society and European Respiratory Society Statement (ATS/ERS). Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**159**(Supplement):S1–40.
- Richardson RS, Sheldon J, Poole DC, et al. Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**159**:881–5.
- Oelberg DA, Kacmarek RM, Pappagianopoulos PP, et al. Ventilatory and cardiovascular responses to inspired He-O_2 during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**158**:1876–82.
- Simon M, LeBlanc P, Jobin J, et al. Limitation of lower limb VO_2 during cycling exercise in COPD patients. *J Appl Physiol* 2001;**90**:1013–9.
- Aliverti A, Macklem P. How and why exercise is impaired in COPD. *Respiration* 2001;**68**:229–39.
- Peters MM, Webb KA, O'Donnell DE. Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. *Thorax* 2006;**61**:559–67.
- Bianchi L, Foglio K, Pagani M, et al. Effects of proportional assist ventilation on exercise tolerance in COPD patients with chronic hypercapnia. *Eur Respir J* 1998;**11**:422–7.
- Hawkins P, Johnson LC, Nikolettou D, et al. Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. *Thorax* 2002;**57**:853–9.
- Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. *Can J Appl Physiol* 2004;**29**:463–87.
- Younes M. Proportional assist ventilation, a new approach to ventilatory support. *Am Rev Respir Dis* 1992;**145**:114–20.
- Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
- Younes M, Puddy A, Roberts D, et al. Proportional assist ventilation. Results of an initial clinical trial. *Am Rev Respir Dis* 1992;**145**:121–9.
- 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.
- 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.
- Neder JA, Nery LE, Castelo A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. *Eur Respir J* 1999;**14**:1304–13.
- Sahlin K. Non-invasive measurements of O_2 availability in human skeletal muscle with near-infrared spectroscopy. *Int J Sports Med* 1992;**13**(Suppl 1):S157–60.
- Kowalchuk JM, Rossiter HB, Ward SA, et al. The effect of resistive breathing on leg muscle oxygenation using near-infrared spectroscopy during exercise in men. *Exp Physiol* 2002;**87**:601–11.
- Bernstein DP. A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale. *Crit Care Med* 1986;**14**:904–9.
- 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.
- Dolmage TE, Goldstein RS. Proportional assist ventilation and exercise tolerance in subjects with COPD. *Chest* 1997;**111**:948–54.
- Hernandez P, Maltais F, Gursahaney A, et al. Proportional assist ventilation may improve exercise performance in severe chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2001;**21**:135–42.
- Bogaard HJ, Hamersma WB, Horsch JL, et al. Non-invasive assessment of cardiac output during exercise in chronic obstructive pulmonary disease: comparison of the CO_2 -rebreathing method and electrical impedance cardiography. *Physiol Meas* 1997;**18**:327–38.
- Bogaard HJ, Dekker BM, Arntzen BW, et al. The haemodynamic response to exercise in chronic obstructive pulmonary disease: assessment by impedance cardiography. *Eur Respir J* 1998;**12**:374–9.
- Light RW, Mintz HM, Linden GS, et al. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. *Am Rev Respir Dis*; **130**:391–5.
- Bhambhani YN. Muscle oxygenation trends during dynamic exercise measured by near infrared spectroscopy. *Can J Appl Physiol* 2004;**29**:504–23.
- Evison H, Cherniack RM. Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 1968;**25**:21–7.
- Takayama T, Shindoh C, Kurokawa Y, et al. Effects of lung volume reduction surgery for emphysema on oxygen cost of breathing. *Chest* 2003;**123**:1847–52.
- Harms CA, Babcock MA, McClaran SR, et al. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 1997;**82**:1573–83.
- Harms CA, Wetter TJ, McClaran SR, et al. Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J Appl Physiol* 1998;**85**:609–18.
- St Croix CM, Morgan BJ, Wetter TJ, et al. Fatiguing inspiratory muscle work causes reflex sympathetic activation in humans. *J Physiol* 2000;**529**:493–504.
- Sexton WL, Poole DC. Effects of emphysema on diaphragm blood flow during exercise. *J Appl Physiol* 1998;**84**:971–9.
- Radegran G. Limb and skeletal muscle blood flow measurements at rest and during exercise in human subjects. *Proc Nutr Soc* 1999;**58**:887–98.