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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 due to increased oxygen delivery (higher cardiac output and/or arterial oxygen content) in patients with chronic obstructive pulmonary disease (COPD).**

***Methods*: Sixteen non-hypoxaemic males (FEV_1= 42.2 ± 13.9 % pred) 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 deoxy-hemoglobyn [HHb], oxi-Hb [O_2Hb], tissue oxygenation index (TOI) and total Hb [Hb_{tot}] in the *vastus lateralis* 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 to sham. 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, i.e., DO_2est remained unchanged with PAV ($p>0.05$). Leg muscle oxygenation, however, was significantly enhanced with PAV as the exercise-related decrease in Δ[O_2Hb]% was lessened and TOI was improved; moreover, Δ[Hb_{tot}]%, an index of local blood volume, was increased compared to 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.**

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INTRODUCTION

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 paid to peripheral muscle abnormalities as adjunct mechanisms to constrain (or even limit) exercise tolerance in this patient population. [as reviewed in ref. 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] were 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 O_2 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.

Therefore, 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 O_2 delivery to the peripheral muscles, i.e., higher cardiac output and/or improved CaO_2.

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METHODS

Subjects

The study population comprised 16 males with clinical and functional diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease criteria, presenting with 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 in the study, the patients were required to be clinically stable for at least 3 months and they were optimized in terms of medical therapy. No patient had used oral steroids in the preceding 6 months. Subjects were also required to present with resting PaO_2 > 60 mmHg at room air and no evidence of severe pulmonary hypertension (estimated systolic pulmonary arterial pressure < 40 mmHg) and/or relevant cardiac dysfunction (including ejection fraction < 60%) as assessed by echodopplercardiography. Patients gave a 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 (CWR) 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 CWR at the previously-defined WR to the limit of tolerance (Tlim). During these tests, they were randomly assigned to receive sham ventilation or the pre-selected levels of PAV.

Non-invasive positive pressure ventilation

Proportional assisted ventilation (PAV) was applied via a tight-fitting, partial-face mask with pressure levels being delivered by a mechanical ventilator (Evita-4™, Draeger Medical AG & Co., Lübeck, Germany). PAV provides ventilatory assistance in terms of flow assist (cm $H_2O/L/s$) and volume assist (cm H_2O/L) which can unload the resistive and elastic burdens, respectively.[11,13] Initially, volume assist was set by increasing the level of assist by 2 cm H_2O/L until "run-away" was demonstrated; in this phase, flow assist was maintained at 1 cm $H_2O/L/s$. Afterwards, flow assist was set by increasing its value by 1 cm $H_2O/L/s$ until "run-away" occurred with volume assist being kept fixed at 2 cm H_2O/L. A fraction (80%) of these values were used initially, with flow and volume assist settings adjusted for patient comfort to avoid "run-away" during exercise (see *Results* for the actual values used during exercise).

Non-invasive sham ventilation was applied by the same equipment using the minimal inspiratory pressure support (5 cmH_2O of inspiratory pressure support and 2 cmH_2O 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.

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Measurements

Pulmonary function

Post-bronchodilator spirometric tests were performed by using the CPF System™ (Medical Graphics Corporation - MGC, St Paul, Minn, USA). Carbon monoxide diffusing capacity (DL_{CO}) was measured by the modified Krogh technique and the static lung volumes were obtained by body plethysmography (Elite System™, MGC.). Observed values were compared to Brazilian standards.[14,15] Arterial partial pressure for oxygen and carbon dioxide were determined in standard anaerobic conditions (PaO_2 and $PaCO_2$, mmHg).

Cardiopulmonary exercise test (CPET)

Symptom-limited cycle ergometric CPET tests were performed using a computer-based exercise system (CardiO_2 System™, MGC). The following data were recorded as mean of 15 seconds: oxygen uptake ($\dot{V}O_2$, mL/min), minute ventilation ($\dot{V}E$, L/min), respiratory rate (RR, rpm), and tidal volume (VT, L). Oxyhemoglobin saturation (SpO_2, %) was determined by pulse oximetry (POX 010-340™, Mediaid Inc., Torrance CA, USA) with its analogical signal being directed to the cardiopulmonary exercise system. From these data, arterial O_2 content was estimated (est) as CaO_2est (mL%)= 1.39[Hb] × SpO_2. Subjects were also asked to rate their "shortness of breath" at exercise cessation using the 0-10 Borg's category-ratio scale.

In the maximum progressive exercise test, the rate of power increment was individually selected (usually 5 to 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. for the adult Brazilian population.[16] As cited, the CWR tests were performed at 70-80% of the previously determined peak WR to the limit of tolerance (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, OH, USA.

Skeletal muscle oxygenation

Skeletal muscle oxygenation profiles of the left *vastus lateralis* 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 fiber optic bundle carried the NIR light produced by the laser diodes to the tissue of interest while a second fiber optic bundle returned the transmitted light from the tissue to a photon detector in the spectrometer. The intensity of incident and transmitted light was recorded continuously and, along with the relevant specific extinction coefficients, used for online estimation and display of the changes from the resting baseline of the concentrations of oxy- ([O_2Hb]), deoxy- ([HHb]), and total ([Hb_{tot}]) hemoglobin. 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 x([O_2Hb]/[Hb_{tot}]). [10,16,17] The values were recorded as a delta (Δ) from baseline in units of μM/cm. In order to reduce intra-

subject variability and improve inter-subject comparability, $\Delta[O_2Hb]$ and $\Delta[HHb]$ values were expressed as % of the maximal value determined on a post-exercise maximal voluntary contraction (MVC) or on early recovery (Δ $[Hb_{tot}]$). Additional methodological considerations on this technique can be found in the *On Line Supplement*.

Central hemodynamics

Cardiac output (L / min) and stroke volume (L) were measured non-invasively throughout the CWR tests using a impedance cardiography device (PhysioFlow PF-05™, Manatec Biomedical, France). These data were also used to estimate O_2 delivery (DO_2est= cardiac output x 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 visualizing the ECG tracing and its first derivative (dECG / dt) and the impedance waveform (ΔZ) with its first derivative (dZ / dt).[20] Additional methodological considerations on this technique can also be found in the *On-Line Supplement*.

Statistical analysis

The SPSS version 13.0 statistical software was used for data analysis (SPSS, Chicago, IL, USA). Results were summarized as mean ± SD or median and ranges 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.

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RESULTS

Population characteristics

Patients had moderate-to-severe airflow obstruction with increased static lung volumes and moderate reductions in D_{LCO}. Seven patients were classified as GOLD stages II, with the remaining patients being considered as GOLD stages III-IV.[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 $\dot{V}Emax/MVV$ ratio (>0.8), was found in all subjects. Eight patients had mild exercise-related oxyhemoglobin 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 are presented in the *On Line Supplement*.

Effects of PAV metabolic, ventilatory and perceptual responses

All patients successfully tolerate the two non-invasive ventilation modes during exercise. The actual values for volume assist and flow assist during PAV were: 5.8 ± 0.9 cmH_2O/L and 3.5 ± 0.8 $cmH_2O/L/s$, respectively. We found that PAV was associated with a significant increase in exercise tolerance compared to sham: 337 ± 189 s *vs*. 273 ± 142 s (p=0.01). In fact, 13/16 patients improved Tlim with PAV compared to sham (Figure 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 between-intervention differences in breathing pattern . In addition, leg effort and breathlessness at isotime and corrected for Tlim were significantly reduced with PAV compared to sham ventilation (Table 1).

Table 1. Effects of 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

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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)*

Definition of abbreviations: $\dot{V}O_2$= oxygen consumption; $\dot{V}CO_2$= carbon dioxide output; RER= respiratory exchange ratio; $\dot{V}E$= minute ventilation; MVV= maximal voluntary ventilation.
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).

Systemic oxygen delivery and muscle oxygenation

There were no significant effects of PAV on the cardiovascular responses compared to sham. As shown in Table 2, stroke volume and cardiac output did not differ between the interventions at isotime and at Tlim. In similarity with the maximal exercise test, only 8 patients had mild changes in SpO_2 (exercise-rest= -4% to 3%). There was also no significant change in SpO_2 with PAV compared to sham ventilation (Table 2): the median (range) of the intra-subject difference in SpO_2 between the two interventions throughout exercise was 0% (-2 to 2%). Consequently, estimated systemic O_2 delivery (DO_2est= cardiac output x CaO_2est) remained unchanged with PAV at isotime and Tlim (Table 2): the median (range) of the intra-subject difference in DO_2est between the two interventions was 0.12 L / min (-0.20 to 0.18 L / min).

In relation to muscle oxygenation by NIRS, PAV was associated with lower Δ[HHb] at 75% isotime, at isotime and at Tlim: these changes were accompanied by a significant reduction in the exercise-related decrease in Δ[O_2Hb] (Table 2; Figures 2A and 2B, respectively). Consequently, TOI was improved with PAV at these time points (Figure 2C). Moreover, Δ[Hb_{TOT}], an index of local blood volume, was also significantly increased with PAV (Figure 2D). Consistent with these data, lactate values corrected for Tlim were reduced with PAV compared to sham (Table 2).

Table 2. Effects of PAV and sham ventilation on oxygen transport / utilization 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**
Cardiovascular/Hemodynamics				
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

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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
Systemic oxygenation				
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_2est (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_2est (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
Leg muscle oxygenation				
Δ[HHb] (% MVC)	88.7 ± 15.4	72.9 ±16.4*	90.7 ± 14.1	71.8 ± 15.9*
Δ[O_2Hb] (% 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*
Blood Lactate				
Absolute (μMol / L)	-	-	3.8±1.3	3.9±1.2
Lactate / time (μMol / L / min)	-	-	0.99±0.40	0.85±0.35*

Definition of abbreviations: SpO_2= oxyhemoglobin saturation by pulse oximetry; CaO_2est= estimated arterial oxygen content; DO_2est= estimated oxygen delivery; MVC= maximum voluntary contraction; HHb= reduced hemoglobin; O_2Hb= oxyhemoglobin; Hb_{TOT}= total hemoglobin; TOI= tissue oxygenation index

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

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DISCUSSION

This study demonstrated that respiratory muscle unloading during exercise (PAV) can improve leg muscle oxygenation ($\Delta[O_2Hb]$ and TOI) and local blood volume ($\Delta[Hb_{TOT}]$) in patients with moderate-to-severe COPD. These findings, however, were not related to enhanced systemic DO_2 (cardiac output x CaO_2) 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 to reduce 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 to reduce inspiratory muscle work in patients with COPD; in addition, it showed to be more tolerable for these patients, allowing them to exercise for longer and at significantly higher intensities.[9,22,23] Unfortunately, however, we were unable to measure directly the work of breathing as small air leaks have profound effects on the levels of assistance by PAV. Therefore, an esopahageal baloon could not be placed in as PAV had to be delivered through a tight-fitting facial mask by the system used in the present study.

We used NIRS to continuously follow the muscle oxygenation patterns during exercise.[10,17] Although this technique is not able to differentiate between the signal attenuation due to Hb and myoglobin, this confounding factor has been estimated as 10% of the whole Hb 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 intra-subject 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 stable during exercise in these patients. Considering, however, the controversies on the absolute accuracy of this methodology in patient populations,[24,25] we firstly assured that the system was responsive to small changes in the metabolic demand and the observed values were commensurate to the expected values from the submaximal Δ cardiac output -ΔVO_2 relationship (see the *On Line Supplement*).[4,21] In addition, the stroke volume signal remained stable even when dynamic lung hyperinflation was induced in a sub-group of patients (see the *On Line Supplement*).

Energy supply to the locomotor muscles in COPD

It is widely recognised that skeletal muscle oxygenation depends on the dynamic balance between O_2 delivery and utilization.[10] In the present study, PAV was associated with a blunted decrease in exercise $\Delta[O_2Hb]$% with a consequent

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improvement in TOI; in addition, $\Delta[Hb_{TOT}]$%, 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 $\dot{V}O_2$ was higher after respiratory muscle unloading (Table 1). This finding seems to indicate that peripheral muscle O_2 consumption had been limited by supply before respiratory unloading in these patients and this more than counterbalanced the potential reductions in respiratory muscle $\dot{V}O_2$ 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 intra-pulmonary gas exchange and/or enhanced central haemodynamic adjustments to exercise. These findings imply that an alternative mechanism should be sought in order to explain the improvement in leg O_2 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 respiratory muscles work during exercise may require up to 50% of body oxygen uptake ($\dot{V}O_2$) [27,28] and it is plausible that a fraction of the cardiac output can be diverted from the locomotor muscles to attend the increased energy demands of the ventilatory pump.[3-6] In normal subjects, a series of elegant experiments from Dempsey´s group have demonstrated that a respiratory muscle fatigue-induced metaboreflex could increase sympathetic vasoconstrictor outflow reducing locomotor muscles perfusion during exercise, i.e., a blood flow "stealing" effect.[29-31] The "stealing" hypothesis, therefore, is attractive to explain our findings: improvement in the intra-diaphragmatic 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

In the present study, we found that a strategy targeted to reduce the work of breathing and dyspnoea showed to be effective in improving the oxygenation status of the leg muscles. These results, therefore, emphasise the multi-factorial nature of exercise impairment in patients with COPD and they provide a rationale for the improvement in leg fatigability with selected interventions which primarily act upon the respiratory system. Peters et al. for instance, recently described that the combination of bronchodilators and oxygen were superior to each on isolation in order to reduce leg effort scores during exercise in normoxic patients with COPD.[7] Other studies with heliox breathing and non-invasive positive pressure ventilation also reported 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 aimed to evaluate the impact of interventions upon the mechanical-ventilatory

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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 intra-muscular changes in perfusion.[33] An intra-arterial catheter was not inserted in our patients and arterial oxygen content (CaO_2) was estimated from continuous SpO_2 readings. We believe that this provided an acceptable surrogate of the true CaO_2 in this non-hypoxaemic patients. We also could not perform IC maneuvers 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 disadaptation of non-invasive ventilation. Our results, therefore, should not be extrapolated for more hyperinflated patients than those evaluated in the present study though the higher oxygen cost of breathing may indicate that the "stealing" phenomenon can also be operative in that specific sub-population. 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.

Conclusions

Respiratory muscle unloading, via PAV, was associated with increased peripheral muscle oxygenation under stable systemic O_2 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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FIGURE LEGENDS

Figure 1. Effects of proportional assisted ventilation (PAV) and sham ventilation on the tolerance to high-intensity constant work rate exercise (Tlim) in a group of patients with moderate to severe COPD (N= 16).

Figure 2. A comparative analysis between the effects of proportional assisted ventilation (PAV, *closed symbols*) and sham ventilation (*open symbols*) on peripheral muscle oxygenation (*vastus lateralis*) as determined by near-infrared spectroscopy during submaximal exercise (N= 16). Note that PAV lowered Δ[HHb]% and lessened the exercise-related decrease in Δ[O_2Hb]% at 75% isotime and at exercise cessation (*panels A* and *B*, respectively); in addition, higher values of Δ[HbTOT]% were found with active treatment at these time points (*panel C*). Consistent with these data, exercise-related decrease in TOI was lessened with PAV compared to sham (*panel D*).

Footnotes

Data are mean (SE). Definition of abbreviations: HHb= reduced hemoglobyn; O_2Hb= oxyhemoglobin; HbTOT= total hemoglobin; TOI= tissue oxygenation index.

***p<0.05 for between-intervention differences at a given time point (repeated measures one-way ANOVA).**

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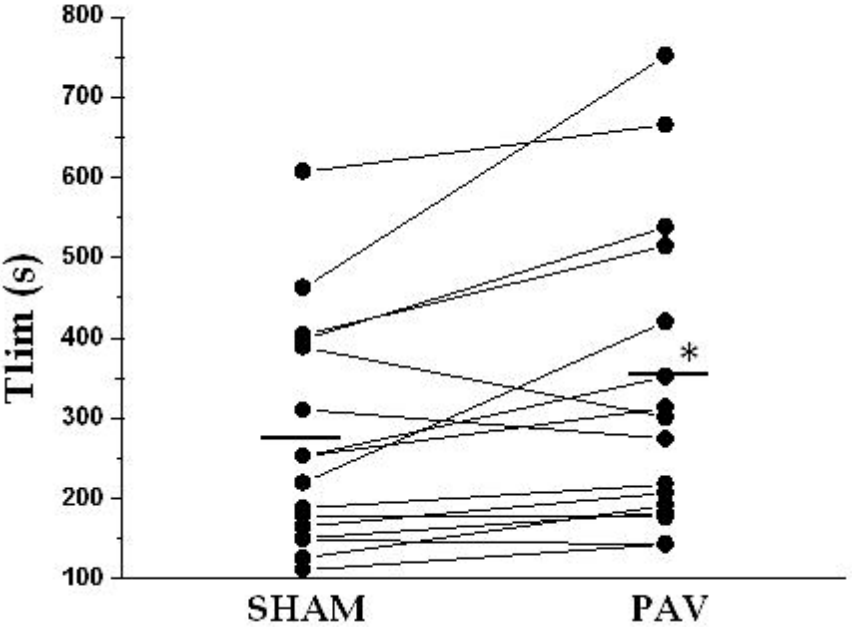
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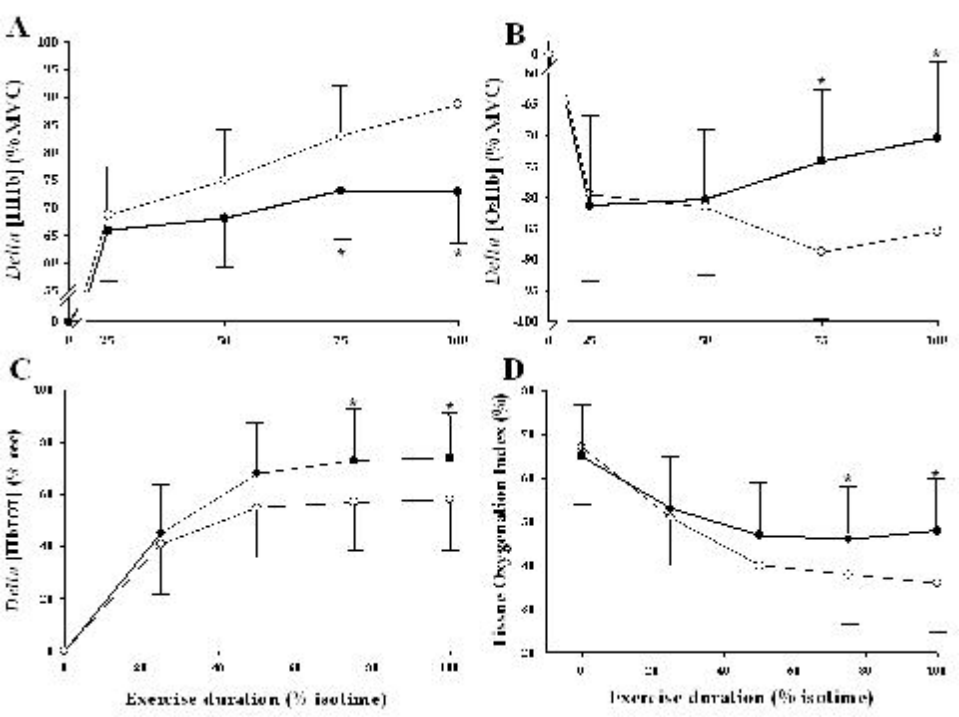
Tlim (s)
*
SHAM
PAV


A
B
C
D
Exercise duration (% isotime)
Exercise duration (% isotime)

ON-LINE SUPPLEMENT

Respiratory Muscle Unloading Improves Leg Muscle Oxygenation During Exercise in Patients with COPD

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METHODS

Subjects

The study population comprised 16 males with clinical and functional diagnosis of COPD according to the Global Initiative for Obstructive Lung Disease criteria, presenting with FEV_1/FVC ratio < 0.7 and post-bronchodilator FEV_1 < 60% predicted.[1] The patients were referred from the COPD outpatients clinic of our Institution. Before entering in the study, the patients were required to be clinically stable for at least 3 months and they were optimized in terms of medical therapy. No patient had used oral steroids in the preceding 6 months. Subjects were also required to present with resting PaO_2 > 60 mmHg at room air and no evidence of severe pulmonary hypertension (estimated systolic pulmonary arterial pressure < 40 mmHg) and/or relevant cardiac dysfunction (including ejection fraction < 60%) as assessed by echodopplercardiography. Patients gave a 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 (CWR) 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 CWR at the previously-defined WR to the limit of tolerance (Tlim). During these tests, they were randomly assigned to receive sham ventilation or the pre-selected levels of PAV.

Non-invasive positive pressure ventilation

Proportional assisted ventilation (PAV) was applied via a tight-fitting, partial-face mask with pressure levels being delivered by a mechanical ventilator (Evita-4™, Draeger Medical AG & Co., Lübeck, Germany). In this ventilation mode, the ventilator delivers pressure that is proportional to patient's spontaneous effort.[2,3] PAV provides ventilatory assistance in terms of flow assist (cm $H_2O/L/s$) and volume assist (cm H_2O/L) which can unload the resistive and elastic burdens, respectively.[11,13] PAV was set individually for each patient using a method described previously.[4,5] Initially, volume assist was set by increasing the level of assist by 2 cm H_2O/L until "run-away" was demonstrated; in this phase, flow assist was maintained at 1 cm $H_2O/L/s$. Afterwards, flow assist was set by increasing its value by 1 cm $H_2O/L/s$ until "run-away" occurred with volume assist being kept fixed at 2 cm H_2O/L. A fraction (80%) of these values were used initially, with flow and volume assist settings adjusted for patient comfort to avoid "run-away" during exercise (see *Results* for the actual values used during exercise).

Non-invasive sham ventilation was applied by the same equipment using the minimal inspiratory pressure support (5 cmH_2O of inspiratory pressure support and 2 cmH_2O 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)

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under use: this was accomplished by visually isolating the ventilator and its monitor from them.

Measurements

Pulmonary function

Post-bronchodilator spirometric tests were performed by using the CPF System™ (Medical Graphics Corporation - MGC, St Paul, Minn, USA). Carbon monoxide diffusing capacity (DL_{CO}) was measured by the modified Krogh technique and the static lung volumes were obtained by body plethysmography (Elite System™, MGC.). Observed values were compared to Brazilian standards.[6,7] Arterial partial pressure for oxygen and carbon dioxide were determined in standard anaerobic conditions (PaO_2 and $PaCO_2$, mmHg).

Cardiopulmonary exercise test (CPET)

Symptom-limited cycle ergometric CPET tests were performed using a computer-based exercise system (CardiO$_2$ System™, MGC) with breath-by-breath analysis of metabolic, ventilatory, and cardiovascular variables. The following data were recorded as mean of 15 seconds: oxygen uptake ($\dot{V}O_2$, mL/min), minute ventilation ($\dot{V}E$, L/min), respiratory rate (RR, rpm), and tidal volume (VT, L). On a preliminary phase of the study, we evaluated whether PAV would interfere with the pulmonary gas exchange measurements compared to sham non-invasive ventilation (N= 5). We were unable to identify significant differences on $\dot{V}O_2$ either at rest or during CWR exercise (50 W) ($p>0.05$). However, carbon dioxide output ($\dot{V}CO_2$) was significantly lower with PAV (up to 300 mL/min); therefore, $\dot{V}CO_2$ values were not considered for analysis. Oxyhemoglobin saturation (SpO_2, %) was determined by pulse oximetry (POX 010-340™, Mediaid Inc., Torrance CA, USA) with its analogical signal being directed to the cardiopulmonary exercise system. From these data, arterial O_2 content was estimated (est) as CaO_2est (mL%)= 1.39[Hb] × SpO_2. In order to improve data reliability, continuous SpO_2 readings were revised for the detection of aberrant points. Subjects were also asked to rate their "shortness of breath" at exercise cessation using the 0-10 Borg's category-ratio scale: symptom scores were expressed in absolute values and corrected for exercise duration.

In the maximum progressive exercise test, the rate of power increment was individually selected (usually 5 to 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. for the adult Brazilian population.[8] As cited, the CWR tests were performed at 70-80% of the previously determined peak WR to the limit of tolerance (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, OH, USA): the values were also corrected for exercise duration.

Skeletal muscle oxygenation

Skeletal muscle oxygenation profiles of the left *vastus lateralis* 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.[9,10] Briefly, one fiber optic bundle carried

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the NIR light produced by the laser diodes to the tissue of interest while a second fiber optic bundle returned the transmitted light from the tissue to a photon detector in the spectrometer. The intensity of incident and transmitted light was recorded continuously and, along with the relevant specific extinction coefficients, used for online estimation and display of the changes from the resting baseline of the concentrations of oxy- ([O_2Hb]), deoxy- ([HHb]), and total ([Hb_{tot}]) hemoglobin. 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 x([O_2Hb]/[Hb_{tot}]).[9-11] Due to the uncertainty of the differential pathlenght factor (DPF) for the *quadríceps*, we did not utilize a DPF in the present study. Therefore, the values were recorded as a delta (Δ) from baseline in units of μM/cm. In order to reduce intra-subject variability and improve inter-subject comparability, Δ[O_2Hb] and Δ[HHb] values were expressed as % of the maximal value determined on a post-exercise maximal voluntary contraction (MVC) or on early recovery (Δ [Hb_{tot}]).

In the present study, a set of optodes was placed at the belly of the *vastus lateralis* midway between the lateral epicondyle and greater trochanter of the femur. The optodes were housed in an optically dense plastic holder, thus ensuring that the position of the optodes, relative to each other, was fixed and invariant. The optode assembly was secured on the skin surface with tape, and then covered with an optically dense, black vinyl sheet, thus minimizing the intrusion of extraneous light and loss of NIR light.[10] Before the experiments, we obtained the coefficient of variation (CV) for each of the studied variables in a representative group of patients with COPD (N= 10), with actual values being: 8.7 % for Δ[O_2Hb], 4.1 % for Δ[HHb], 4.3% for (Hb_{tot}), and 6.5% for TOI. In order to test, the sensitivity of the main NIRS variables to improved muscle perfusion, 5 patients performed an exercise bout at 70-80% peak WR on a separate day. In this test, a cuff was placed around the proximal thigh and its pressure increased to 30 mmHg above the arterial systolic pressure after 2 min of exercise. After stabilization of the signals, the highest Δ[HHb] value was considered to represent maximal deoxygenation (“100%”); similarly, the lowest Δ[O_2Hb] and Δ[HbTOT] values during occlusion were assumed to represent the “zero” point. The pressure was then subsequently reduced every 30 s to progressively lower values until a pressure of 30 mmHg below the arterial systolic pressure was reached. We found that enhanced muscle perfusion was associated with a linear decrease in Δ[HHb] which was accompanied by greater increases in Δ[O_2Hb], i.e., Δ[HbTOT] increased substantially with improved muscle perfusion (Figure 1).

Central hemodynamics

Cardiac output (L/min) and stroke volume (L) were measured non-invasively throughout the CWR tests using a impedance cardiography device (PhysioFlow PF-05™, Manatec Biomedical, France). These data were also used to estimate O_2 delivery (DO_2est= cardiac output x CaO_2est, L/min). The PhysioFlow device and its methodology have been thoroughly described elsewhere.[12] 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 visualizing the ECG tracing and its first derivative (dECG/dt) and the impedance waveform (ΔZ) with its first derivative (dZ/dt).[12] Before the experimental phase of

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the study, we calculated the coefficient of variation (CV) for cardiac output and stroke volume (3.3% and 4.1 %, respectively). We tested the system sensitivity to small changes in cardiac output during a series of four constant WR exercise tests performed within a representative range of exercise intensities. Therefore, after a baseline of 50 W, power was increased to 55 W, 60 W, 65 W and 70 W on each separate test. These work rates provided approximated increases in $\dot{V}O_2$ above baseline of 50 ml/min, 100 mL/min, 150 mL/min and 200 mL/min, respectively. We then observed whether the changes in cardiac output were consistent with those values expected from the submaximal cardiac output–$\dot{V}O_2$ found in previous studies in this population (~5 L of cardiac output per L of $\dot{V}O_2$).[13,14] As shown in Figure 2, the system was sensitive to detect small changes in cardiac output (~ 250 mL/min) with acceptable accuracy (within ±10% for all readings). Moreover, we investigated if changes in the operating lung volumes could interfere in cardioimpedance signals. This was performed by having the subjects performed three 15-sec maximal voluntary ventilation maneuvers at a respiratory rate of 50 respirations/minute with inspiratory capacity (IC) being measured before and after hyperventilation. Despite a reduction in IC of 345 ± 78 mL (suggesting the development of dynamic hyperinflation and, probably, increased intra-thoracic gas volume), there were no discernible changes in stroke volume (1.7 ± 0.3 %) .

Statistical analysis

The SPSS version 13.0 statistical software was used for data analysis (SPSS, Chicago, IL, USA). Results were summarized as mean ± SD or median and ranges 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.

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RESULTS

Population characteristics

Resting and exercise characteristics are presented in Table 1. On average, patients had moderate-to-severe airflow obstruction with increased static lung volumes and moderate reductions in D_LCO. Seven patients were classified as GOLD stages II, with the remaining patients being considered as GOLD stages III-IV.[8] 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 $\dot{V}Emax/MVV$ ratio (>0.8), was found in all subjects. Eight patients had mild exercise-related oxyhemoglobin desaturation (peak SpO_2 ranging from 89 to 86%). Breathlessness and leg effort were similarly described as the exercise limiting symptoms (Table 1).

Table 1. Patients characteristics at rest and maximal exercise (N=16).

Variables	Values
Demographic/ Anthropometric	
Age (yrs)	59.4 ±6.3
Body mass index (kg/m^2)	24.6 ± 4.4
Pulmonary function	
FEV_1 (L)	1.32 ± 0.43
FEV_1 (% pred)	42.2 ± 13.9
FVC (% pred)	83.1 ± 13.5
FEV_1/FVC	42.6 ± 15.1
TLC (% pred)	120.3 ± 25.8
RV (% pred)	173.9 ± 53.9
RV/TLC	47.3 ± 9.7
IC (% pred)	85.7 ± 18.8
D_LCO (% pred)	47.3 ± 12.5
P_aO_2 (mmHg)	70.4 ± 7.3
SaO_2 (%)	94.3 ± 2.7
P_aCO_2 (mmHg)	39.2 ± 4.9
Maximal exercise	
Peak $\dot{V}O_2$ (% pred)	60.9 ± 23.7
Peak $\dot{V}O_2$ (mL/min)	1272 ± 360
Power (W)	85 ± 30
$\dot{V}E$ (L/min)	42.9 ± 14.9
$\dot{V}E$ /MVV	0.86 ± 0.13
Respiratory rate (bpm)	29 ± 4
Tidal volume (L)	1.43 ± 0.43
Heart rate (% pred)	84.4 ± 9.2
Dyspnoea scores	7 (3-10)
Leg effort scores	7 (0-10)

Definition of abbreviations: FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; TLC= total lung capacity; RV= residual volume; IC= inspiratory capacity; D_LCO= lung diffusing capacity for carbon monoxide; Pa= arterial pressure; Sa= arterial saturation; $\dot{V}O_2$=

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oxygen consumption; $\dot{V}_E$= minute ventilation; MVV= maximal voluntary ventilation. Mean (SD) with exception of symptoms (median and range).

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FIGURE LEGENDS

Figure 1. Effects of increased muscle perfusion during exercise on the variables of interest measured by near infrared spectroscopy in a subgroup of patients with COPD (N= 5). After a cuff had been placed around the proximal thigh, the pressure was increased to 30 mmHg above the arterial systolic pressure (*S*). The highest change (Δ) in deoxy-hemoglobin ([HHb], closed circles) was assumed to represent maximal deoxygenation ("100%") and the lowest values for Δ oxy-Hb ([O_2Hb], open circles) and Δ total Hb ([Hb_{TOT}], open squares) were set as "0%". Then, *S* was reduced to progressively lower values every 30 s. Note the linear decrease in Δ[HHb] with improved muscle perfusion which was accompanied by greater increases in Δ[O_2Hb],i.e., Δ[Hb_{TOT}] increased in parallel with local blood perfusion.

Figure 2. Comparison between changes (Δ) in predicted and observed cardiac output values (L/min) by bioelectrical impedance cardiography (PhysioFlow PF-05™, Manatec Biomedical, France) in response to four constant work rate exercise tests in 10 patients with moderate-to-severe COPD (see text for further elaboration). Changes in cardiac output were predicted from the Δ cardiac output–Δoxygen uptake submaximal relationship that has been previously reported in these patients.[4,21] Note that the differences ranged between –5 to 8 % of the predicted value, independent of the exercise intensity.

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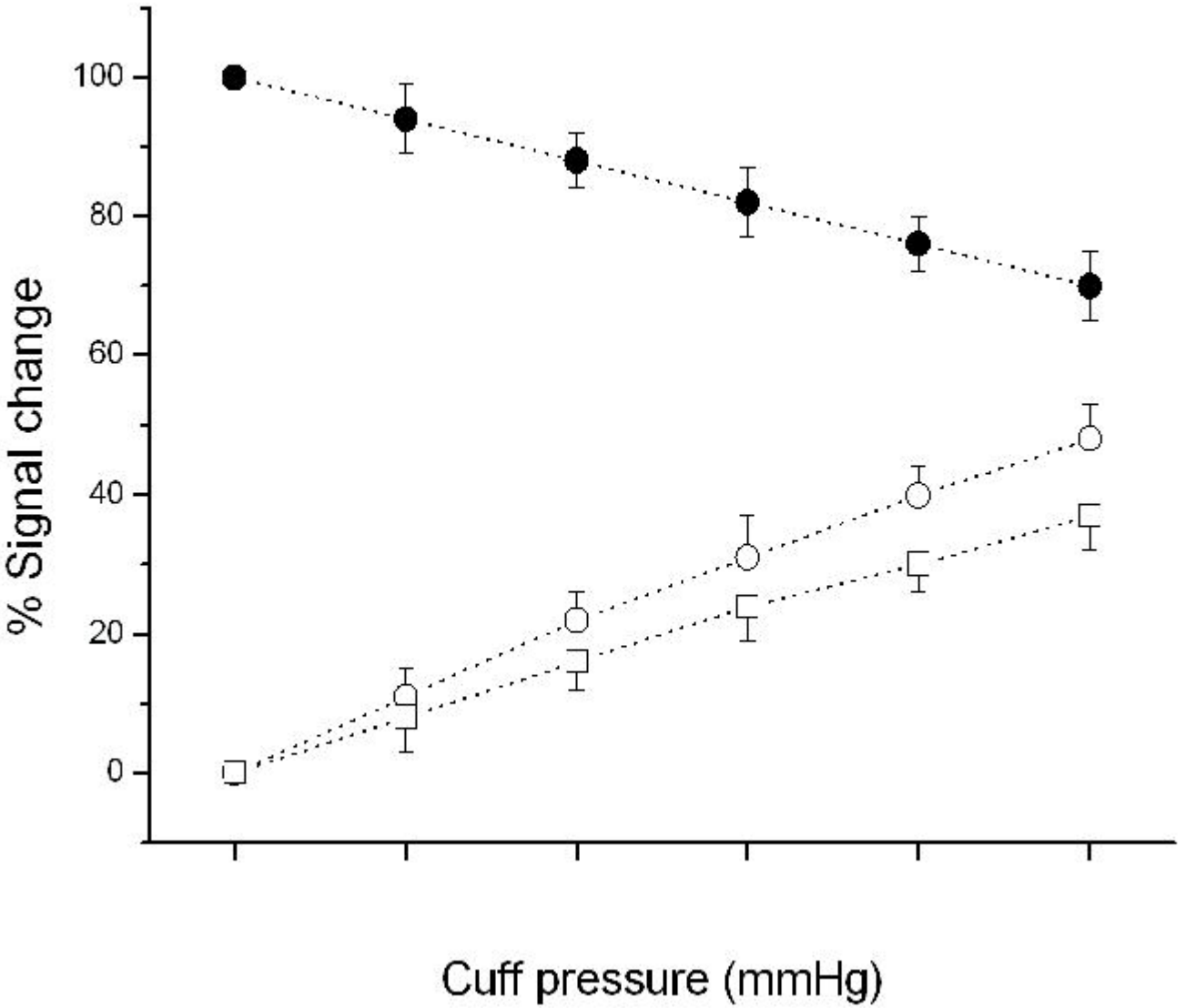
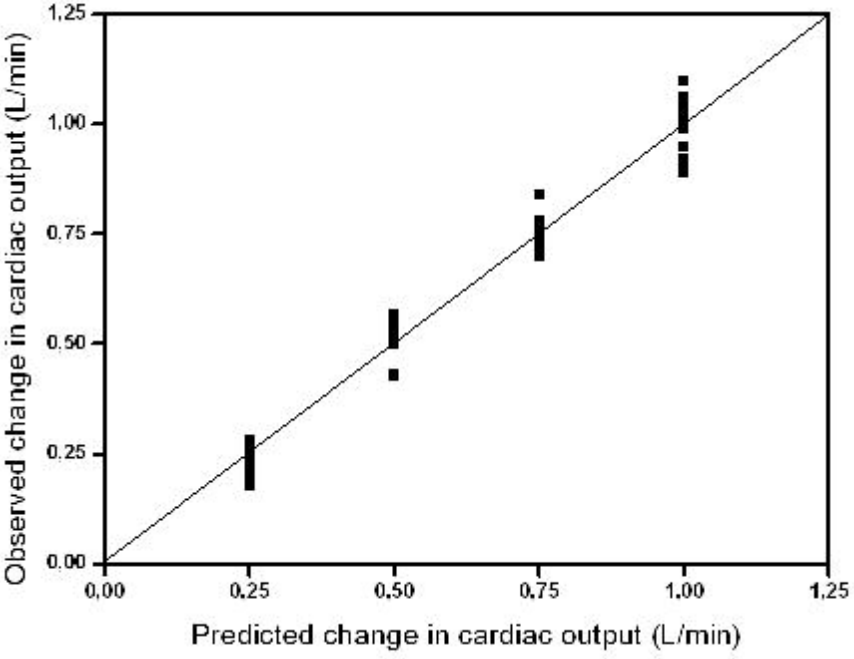

100
80
60
40
20
0
% Signal change
Cuff pressure (mmHg)


1.25
1.00
0.75
0.50
0.25
0.00
Observed change in cardiac output (L/min)
0.00
0.25
0.50
0.75
1.00
1.25
Predicted change in cardiac output (L/min)