

## Effect of expiratory loaded breathing during moderate exercise on intercostal muscle oxygenation

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### ABSTRACT

**Background:** In patients with obstructive lung disease, maintaining adequate ventilation during exercise may require greater contraction of the respiratory muscles, which may lead to a compression of muscle capillaries. Furthermore, dynamic hyperinflation (DH) is frequent during exercise in these patients, as it allows to reach higher expiratory flows and to satisfy respiratory demand. However, in such situation, intercostal muscles are likely to be stretched, which could affect the diameter of their capillaries. Thus, in a context of high level of expiratory resistance, intercostal muscle oxygenation may be disturbed during exercise, especially if DH occurs.

**Methods:** Twelve participants (22±2 years) performed two sessions of moderate exercise (20 min) by breathing freely with and without a 20-cmH<sub>2</sub>O expiratory threshold load (ETL). Tissue saturation index (TSI) and concentration changes from rest ( $\Delta$ ) in oxygenated ([O<sub>2</sub>Hb]) and total haemoglobin ([tHb]) were measured in the seventh intercostal space using near-infrared spectroscopy. Respiratory, metabolic and cardiac variables were likewise recorded.

**Results:** Throughout exercise, dyspnea was higher and TSI was lower in ETL condition than in control ( $p < 0.01$ ). After a few minutes of exercise,  $\Delta$  [O<sub>2</sub>Hb] was also lower in ETL condition, as well as  $\Delta$  [tHb], when inspiratory capacity started to be reduced ( $p < 0.05$ ). Changes in [O<sub>2</sub>Hb] and dyspnea were correlated with changes in expiratory flow rate ( $V_t/T_e$ ) ( $r = -0.66$  and  $0.66$ , respectively;  $p < 0.05$ ).

**Conclusion:** During exercise with ETL, impaired muscle oxygenation could be due to a limited increase in blood volume resulting from strong muscle contraction and/or occurrence of DH.

**Key words:** Intercostal muscle oxygenation; NIRS; expiratory threshold load; exercise; dynamic hyperinflation.

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## Introduction

Obstructive lung diseases are characterized by reduced maximal expiratory flows due to high levels of airway resistance. Physical capacity and self-reported quality of life in patients are impaired but regular physical activity can improve the trend [1,2]. However, exercise tolerance may be strongly limited, as a consequence of reduced ventilatory capacities, systemic alterations, comorbidities and deconditioning [3].

Expiratory flow limitation (EFL) and dynamic hyperinflation (DH) are the main respiratory consequences of obstructive lung diseases. EFL is defined by the inability to increase expiratory flow at a given lung volume despite an increase in driving pressure [4]. Higher flows can be generated due to DH, as tidal breathing is shifted to higher pulmonary volume. This rearrangement occurs frequently during exercise in patient with airway obstruction [5,6]. However, DH increases the work of inspiratory muscles [7,8] and can exacerbate dyspnea [9,10].

In patients with obstructive lung disease, the power produced by respiratory muscles is likely to be raised in order to counteract the respiratory load [11,12]. If DH occurs in addition, intercostal muscles could be stretched [13], which may squeeze blood vessels [14,15]. Thus, in a context of high level of expiratory resistance, blood perfusion may be altered in intercostal muscles during exercise, leading to impaired intercostal muscle oxygenation and metabolic imbalance. A few previous studies have investigated these changes in patients with airway obstruction [16] and in healthy subjects constrained by an external expiratory resistance [17]. However, the involvement of EFL and DH on the alteration of intercostal muscle blood perfusion during exercise remains to be specified.

The aim of this study was to shed light on ventilatory muscle adaptations facing up to high expiratory load and to its own consequence: dynamic hyperinflation, this situation being frequently observed during exercise in obstructive lung diseases. We evaluated the effect of a 20-cmH<sub>2</sub>O expiratory threshold load (ETL) on intercostal muscle oxygenation during continuous moderate exercise in healthy subjects. Tissue oxygenation was measured using near-infrared spectroscopy (NIRS) and intercostal muscles were investigated. Impaired oxygenation was expected in the intercostal muscles during exercise with ETL, as were correlations between DH, tissue oxygenation and dyspnea.

## Design and Methods

### Participants

Twelve healthy active men (22±2 years) were included in this study. Anthropometric and pulmonary function data are given in Table 1. All subjects had normal pulmonary function values [18] and skinfold <20 mm at the seventh left intercostal space [19].

### Study protocol

#### Experimental protocol

Three sessions were scheduled. During the first session, a submaximal incremental exercise test (50 W; +30 W each 2 min) was performed with a cycle ergometer (Corvival PET, Lode B.V., Groningen, Netherlands) up until 70% of the age-predicted maximal heart rate (208-0.7 \* age) [20]. The workload carried out at the target heart rate was imposed in the following two sessions (target workload).

At the beginning of the protocol in the second and third sessions, subjects were studied for 3 minutes, seated on the cycle (baseline). Afterwards, a 20-cmH<sub>2</sub>O expiratory threshold load (ETL, Threshold PEP, Respironics Inc., Murrysville, PA, USA) or a tube with an equivalent dead space and diameter as the ETL (placebo tube) was applied at the mouth for 5 min (rest). Immediately after, subjects cycled for 25 min at 60±5 rpm (detailed in Figure 1). Intense physical exercise was not allowed 24 hours before the experimentation. The second and third sessions were randomly counterbalanced, separated by 7 days and scheduled at the same time of the day.

### Measurements and materials

**Anthropometry.** Skinfold was assessed at the seventh left intercostal space with a skinfold caliper (Harpender, British Indicators Ltd., St. Albans, England) and a whole-body bioelectrical impedance technique was used to assess body fat mass (Tanita BC-418-MA, Tanita Corporation, Tokyo, Japan).

**Pulmonary function tests.** Slow and forced vital capacities (SVC and FVC, respectively) were evaluated at each session (Metalyzer-3B, Cortex Biophysik GmbH, Leipzig, Germany) according to the ATS/ERS Task Force recommendations [21]. At the second and third sessions, EFL was measured several times during the protocol by the technique described by Johnson *et al.* [22]. Spontaneous flow-volume ( $\dot{V}$ -V) curves measured during the protocol were superimposed on the maximal  $\dot{V}$ -V curve (*i.e.* the reference curve of the day) measured a few minutes before the beginning of the protocol (Figure 1). To obtain this reference curve, at least three FVC maneuvers were performed with ETL or placebo tube after five minutes of adaptation (Figure 1). At the second and third session, IC was likewise measured several times during the protocol (Figure 1) to detect exercise-induced DH [22-24]. Measurements of IC also allowed the device to place correctly the spontaneous  $\dot{V}$ -V curve within the reference curve in order to evaluate EFL. A set of two maximal inspirations was performed at rest and the best maneuver (*i.e.* the one with the highest IC) was chosen as reference IC. During exercise, three single maximal inspirations were performed. A second trial was performed when the first maneuver had been disturbed (*e.g.*, saliva swallowing during the maneuver).

**Table 1. Anthropometric and pulmonary function characteristics.**

	Absolute values	Predicted values (%)
Weight (kg)	72±10	
Height (m)	1.8±0.1	
BMI (kg/m <sup>2</sup> )	23±3	
Body fat mass (%)	14±6	
Left 7 <sup>th</sup> IS ATT (mm)	3.7±1.5	
ERV (L)	1.6±0.3	
IRV (L)	3.1±0.6	
IC (L)	3.9±0.6	
SVC (L)	5.6±0.6	104±10
FEV <sub>1</sub> (L)	4.9±0.6	115±13
FVC (L)	5.8±0.6	116±10
FEV <sub>1</sub> /FVC (%)	85±6	99±7
MMEF <sub>25-75%</sub> (L/sec)	5.3±1.2	110±26

Values are mean ± SD. BMI, body mass index; ERV, expiratory reserve volume; FEV<sub>1</sub>, forced expiratory volume during the first second; FVC, forced vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; IS ATT, intercostal space adipose tissue thickness; MMEF<sub>25-75%</sub>, mean median expiratory flow between 25% and 75% of FVC and SVC, slow vital capacity.

**Intercostal muscle oxygenation.** Near-infrared spectroscopy (NIRS) (Oxymon Mk-III, Artinis Medical Systems, Zetten, The Netherlands) was used to assess the tissue saturation index (TSI) and the concentration changes in oxygenated, deoxygenated and total hemoglobin in the intercostal muscles ( $\Delta [O_2Hb]$ ,  $\Delta [HHb]$  and  $\Delta [tHb]$  respectively) [17,25,26]. The change in response to exercise was calculated from the resting period during which ETL or placebo tube was applied. The optode was placed in the seventh intercostal space, on the left side of the subject, between the midclavicular and the anterior axillary lines. As maximal penetration depth of the light is approximately half of the distance between transmitter and receiver [27], interoptode distance was adjusted between 3.3 and 4.8 cm according to adipose tissue thickness. A differential pathlength factor of 4 was chosen [28]. Wavelengths of 859 and 763 nm were used. Data were recorded at 10 Hz and exported at 1 Hz after running average filtering.

**Ventilatory variables and gas exchanges.** Inspiratory and expiratory times ( $T_i$  and  $T_e$ ) and tidal volume ( $V_t$ ) were measured breath-by-breath using the Metalyzer device (Cortex Biophysik GmbH, Leipzig, Germany). Total respiratory time ( $T_{tot}$ ), inspiratory duty cycle ( $T_i/T_{tot}$ ), breathing frequency (BF) and ventilatory flow ( $\dot{V}_E$ ) were calculated, as mean inspiratory and expiratory flow rates ( $V_t/T_i$  and  $V_t/T_e$ ). Oxygen consumption ( $\dot{V}O_2$ ), carbon dioxide production ( $\dot{V}CO_2$ ) and end-tidal  $CO_2$  pressure ( $P_{et}CO_2$ ) were likewise recorded. Respiratory exchange ratio (RER) and respiratory equivalents in oxygen ( $\dot{V}_E/\dot{V}O_2$ ) and carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ) were calculated.

**Dyspnea.** Perception of dyspnea was assessed using the modified 0-10 Borg-scale, before each IC measurement [29]. Subjects were required to point on the scale the level of their respiratory discomfort.

**Pulse oximetry.** A pulse oximeter (Wrist-Ox2 3150, Nonin

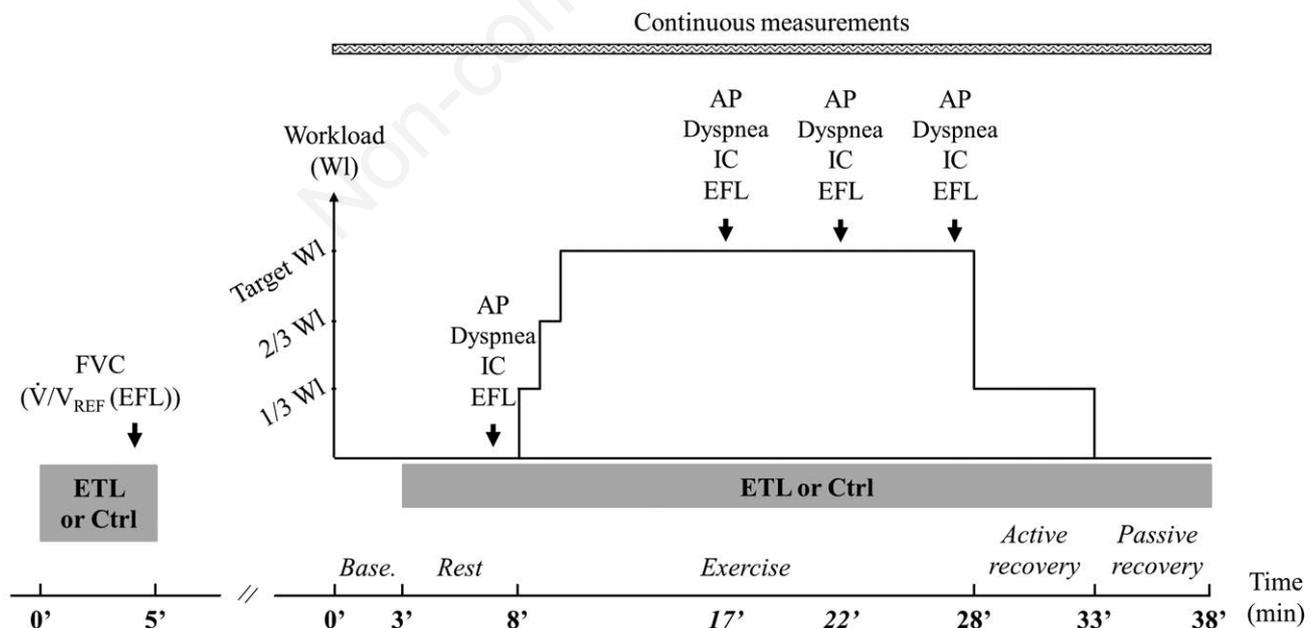
Medical Inc., Plymouth, MN, USA) was placed at the right index to continuously record pulse haemoglobin oxygen saturation ( $SpO_2$ ).

**Cardiovascular parameters.** A PhysioFlow device was used to measure stroke volume (SV), heart rate (HR) and cardiac output ( $\dot{Q}_c$ ) non-invasively and beat-by-beat (PF-05, Manatec Medical, Poissy, France). A sphygmomanometer (Omron-M3, Health Care CO. Ltd, Kyoto, Japan) was used to measure systolic and diastolic blood pressure (SBP and DBP). At rest, mean arterial pressure (MAP) was calculated as follows:  $MAP = DBP + 1/3 (SBP - DBP)$ . During exercise,  $MAP = DBP + 1/2 (SBP - DBP)$ .

### Statistical analysis

Statistical analysis was performed with Statistica (StatSoft Inc., Tulsa, OK, USA). In control and ETL conditions ( $Ctrl_C$  and  $ETL_C$ ), data were analyzed at rest and at the 7<sup>th</sup>, the 12<sup>th</sup>, and the 17<sup>th</sup> min of the constant exercise (7'EX, 12'EX and 17'EX). For variables recorded continuously, mean values were calculated from the last 30 s preceding IC measurements.

Following the verification of parametric conditions, a first two-way repeated measures ANOVA was performed to evaluate the effect of exercise (rest vs 7'EX) according to the conditions ( $Ctrl_C$  vs  $ETL_C$ ). A second ANOVA was conducted to test the effect of exercise duration (7'EX, 12'EX and 17'EX) according to the conditions. A Tukey *post-hoc* analysis was performed when ANOVA was significant. To detect exercise-induced DH, each IC measured during exercise was compared with the corresponding one measured at rest. Hedges' *g* was calculated to define effect size. Correlation coefficients were assessed using the Pearson or Spearman test, according to Gaussian distribution. Values were expressed as mean  $\pm$  standard deviation (SD). Results were considered as significant for a  $p < 0.05$ .



**Figure 1.** Protocol and time measurements. In experimental condition, a 20-cmH<sub>2</sub>O expiratory threshold load (ETL) was applied after three minutes of baseline (Base). In control condition (Ctrl), a tube with an equivalent dead space and diameter as the ETL was applied. With AP, arterial pressure; EFL, expiratory flow limitation; FVC, forced vital capacity; IC, inspiratory capacity and  $\dot{V}/V_{REF}$  curve, reference flow-volume curve obtained from FVC maneuvers. Continuous measurements: intercostal muscle oxygenation and ventilatory, metabolic and cardiac variables.

## Results

Prior to the application of ETL or placebo tube, baseline values were not significantly different between conditions. The exercise workload associated with the target HR ( $135.0 \pm 0.7$  bpm) was  $138 \pm 35$  W.

### Ventilatory variables

Main ventilatory variables are shown in Table 2. At rest, Ti, Ti/Ttot, Vt/Te and dyspnea were higher in ETL<sub>C</sub> than in Ctrl<sub>C</sub> (Ti: 2.5 s vs 1.9 s) while Te was lower (2.1 s vs. 2.6 s). Throughout exercise, Ti, Ti/Ttot and dyspnea were likewise higher with ETL (Ti: 1.5 s vs 1.1 s). Te was 1.3 s regardless of conditions. BF and Vt/Ti were lower with ETL while  $\dot{V}E$  did not change.

IC was not different between conditions at rest. In ETL<sub>C</sub>, IC decreased from rest at the end of the exercise ( $p < 0.05$ ) (Figure 2). EFL was never observed.

### Intercostal muscle oxygenation

As shown in Figure 3, TSI was not different between conditions at rest and decreased in response to exercise in ETL<sub>C</sub> ( $p < 0.001$ ). Throughout exercise, TSI was lower in ETL<sub>C</sub> than in Ctrl<sub>C</sub>.

In Ctrl<sub>C</sub>,  $\Delta [O_2Hb]$  increased during exercise. In ETL<sub>C</sub>,  $\Delta [O_2Hb]$  did not vary during exercise and was lower than in Ctrl<sub>C</sub>.  $\Delta [HHb]$  increased during exercise and tended to be higher in ETL<sub>C</sub> than in Ctrl<sub>C</sub> ( $p = 0.05$ ).  $\Delta [tHb]$  increased during exercise in Ctrl<sub>C</sub> and in ETL<sub>C</sub>. At 17'EX,  $\Delta [tHb]$  was different between the two conditions ( $p < 0.05$ ) as it stopped increasing in ETL<sub>C</sub>.

### Gas exchanges

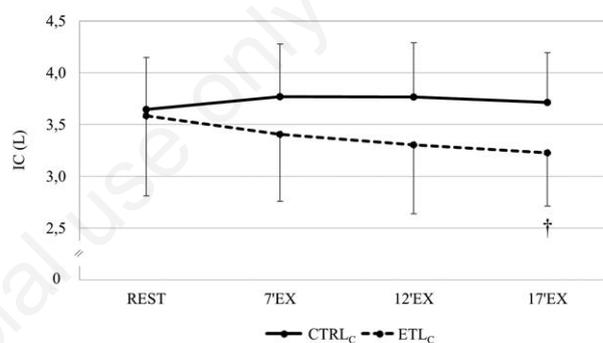
$\dot{V}O_2$  and  $\dot{V}CO_2$  were not affected by ETL. Mean overall  $\dot{V}O_2$  and  $\dot{V}CO_2$  values were 5.2 ml/min/kg and 5.0 ml/min/kg at rest, while at 17'EX, mean values were 29.2 ml/min/kg and 27.3 ml/min/kg. As shown in Table 2, RER,  $\dot{V}E/\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  at rest were higher in ETL<sub>C</sub> than in Ctrl<sub>C</sub> ( $p < 0.05$ ) while  $PetCO_2$  was lower ( $p < 0.01$ ). In response to exercise,  $\dot{V}E/\dot{V}O_2$ ,  $\dot{V}E/\dot{V}CO_2$  and  $SpO_2$  decreased in ETL<sub>C</sub> ( $p < 0.05$ ). Throughout exercise,  $SpO_2$  was lower with ETL<sub>C</sub> than in Ctrl<sub>C</sub> ( $p < 0.05$ ), while the other variables were not different between conditions.

### Cardiovascular variables

HR was higher in ETL<sub>C</sub> than in Ctrl<sub>C</sub> (+12 bpm). SV,  $\dot{Q}_C$  and MAP were not different between conditions.  $\dot{Q}_C$  and MAP were 6.8 L/min and 99 mmHg at rest, while at 17'EX, values were 19.2 L/min and 130 mmHg, respectively.

### Correlations

Correlations are displayed in Figure 4. In ETL<sub>C</sub>, changes in  $[O_2Hb]$  and dyspnea from rest to exercise ( $\Delta = 17'EX_{ETL} - Rest_{ETL}$ ) were correlated with changes in Vt/Te ( $r = -0.66$  and  $r = 0.66$ , respectively;  $p < 0.05$ ). In other words, the more the expiratory flow rate increased in response to exercise, the more  $[O_2Hb]$  was impaired and dyspnea increased. Furthermore, changes in IC from Ctrl<sub>C</sub> to ETL<sub>C</sub> at the end of the exercise ( $\Delta = 17'EX_{ETL} - 17'EX_{CTRL}$ ) were correlated with changes in Vt ( $r = 0.71$ ;  $p < 0.01$ ) and BF ( $r = -0.73$ ;  $p < 0.01$ ).



**Figure 2.** Inspiratory capacity (IC) at rest and at the 7<sup>th</sup> (7'EX), the 12<sup>th</sup> (12'EX) and the 17<sup>th</sup> (17'EX) minute of the steady-state exercise in control and expiratory threshold load conditions (Ctrl<sub>C</sub> and ETL<sub>C</sub>). Values are mean  $\pm$  SD. †different from Rest in the corresponding condition ( $p < 0.05$ ; effect size near to medium). Pairwise *t*-test;  $n = 12$ .

**Table 2.** Ventilatory variables and gas exchanges at rest and during exercise in control and expiratory threshold load conditions (CTRL<sub>C</sub> and ETL<sub>C</sub>).

	CTRL <sub>C</sub>			ETL <sub>C</sub>			Difference between conditions	
	REST	7'EX	17'EX	REST	7'EX	17'EX	At rest	At EX
<b>Ventilatory variables</b>								
Vt (L)	0.9 (0.2)	2.1 (0.4)	2.1 (0.5)	1.3 (0.6)	2.3 (0.6) <sup>‡</sup>	2.2 (0.5)		
BF (c/min)	14.0 (2.4)	25.0 (4.3)	26.2 (3.8)	14.2 (4.3)	21.1 (4.9) <sup>‡</sup>	23.3 (4.8) <sup>§</sup>		*
$\dot{V}E$ (L/min)	11.7 (2.8)	51.7 (9.8)	54.2 (10.2)	17.1 (4.7)	47.3 (8.2) <sup>‡</sup>	49.8 (9.9) <sup>§</sup>		
Ti/Ttot (%)	41.7 (7.3)	46.6 (3.3)	47.1 (3.9)	54.6 (7.3)	53.3 (3.8)	53.1 (5.2)	**	**
Vt/Ti (L/sec)	0.5 (0.1)	1.8 (0.3)	1.9 (0.4)	0.5 (0.2)	1.5 (0.3) <sup>‡</sup>	1.6 (0.4) <sup>§</sup>		*
Vt/Te (L/sec)	0.3 (0.1)	1.6 (0.4)	1.7 (0.4)	0.7 (0.3)	1.7 (0.3) <sup>‡</sup>	1.8 (0.4) <sup>§</sup>	*	
Dyspnea (Borg score)	0.2 (0.3)	1.1 (1.1)	1.5 (1.2)	3.8 (1.2)	5.3 (1.8) <sup>‡</sup>	5.6 (2.1)	**	**
<b>Gas exchanges</b>								
RER	0.89 (0.10)	0.96 (0.03)	0.94 (0.02)	1.01 (0.16)	0.93 (0.05)	0.92 (0.05)	*	
$\dot{V}E/\dot{V}O_2$	24.3 (5.9)	22.7 (2.6)	22.7 (2.6)	33.0 (10.0)	20.8 (3.1) <sup>°</sup>	21.3 (2.9)	*	
$\dot{V}E/\dot{V}CO_2$	27.1 (3.9)	23.6 (2.8)	24.0 (2.7)	32.1 (5.4)	22.2 (2.5) <sup>°</sup>	23.1 (2.7)	*	
$PetCO_2$ (mmHg)	38.3 (3.2)	45.9 (4.8)	44.8 (4.6)	33.1 (4.1)	48.1 (4.3) <sup>‡</sup>	47.4 (4.9) <sup>§</sup>	*	
$SpO_2$ (%)	96.6 (1.3)	95.6 (2.1)	94.6 (1.3)	97.2 (1.0)	93.5 (2.3) <sup>°</sup>	92.8 (2.4)		*

Values are mean (SD). During constant exercise, data were analysed at the 7<sup>th</sup> (7'EX), the 12<sup>th</sup> and the 17<sup>th</sup> min (17'EX). BF, breathing frequency;  $PetCO_2$ , end-tidal  $CO_2$  pressure; RER, respiratory exchange ratio;  $SpO_2$ , pulse haemoglobin oxygen saturation; Ti/Ttot, inspiratory duty cycle; Vt, tidal volume; Vt/Te, expiratory flow rate; Vt/Ti, inspiratory flow rate;  $\dot{V}E$ , ventilatory flow;  $\dot{V}E/\dot{V}CO_2$ , ventilatory equivalent for  $CO_2$  and  $\dot{V}E/\dot{V}O_2$ , ventilatory equivalent for  $O_2$ . \*difference between conditions ( $*p < 0.05$ ;  $**p < 0.001$ ); <sup>°</sup> difference between Rest and 7'EX in ETL<sub>C</sub> only ( $p < 0.05$ ); <sup>‡</sup> difference between Rest and 7'EX in ETL<sub>C</sub> only ( $p < 0.05$ ) or # regardless of condition ( $p < 0.05$ ).

## Discussion

In patients with airway obstruction, high strength must be produced by respiratory muscles to overcome expiratory resistance, especially during exercise. In response to or in prevention of EFL, a shift in  $V_t$  toward higher lung volumes may also stretch intercostal muscles. As a consequence, blood vessels may be compressed. Thereby, a high level of expiratory resistance could lead to impaired tissue oxygenation in these muscles during exercise. To test this hypothesis, intercostal muscle oxygenation was assessed by NIRS while healthy subjects cycled with or without ETL. The main result of this study was that during moderate exercise, intercostal muscle oxygenation was altered when subjects breathed against ETL. DH was suggested to be involved in this impairment.

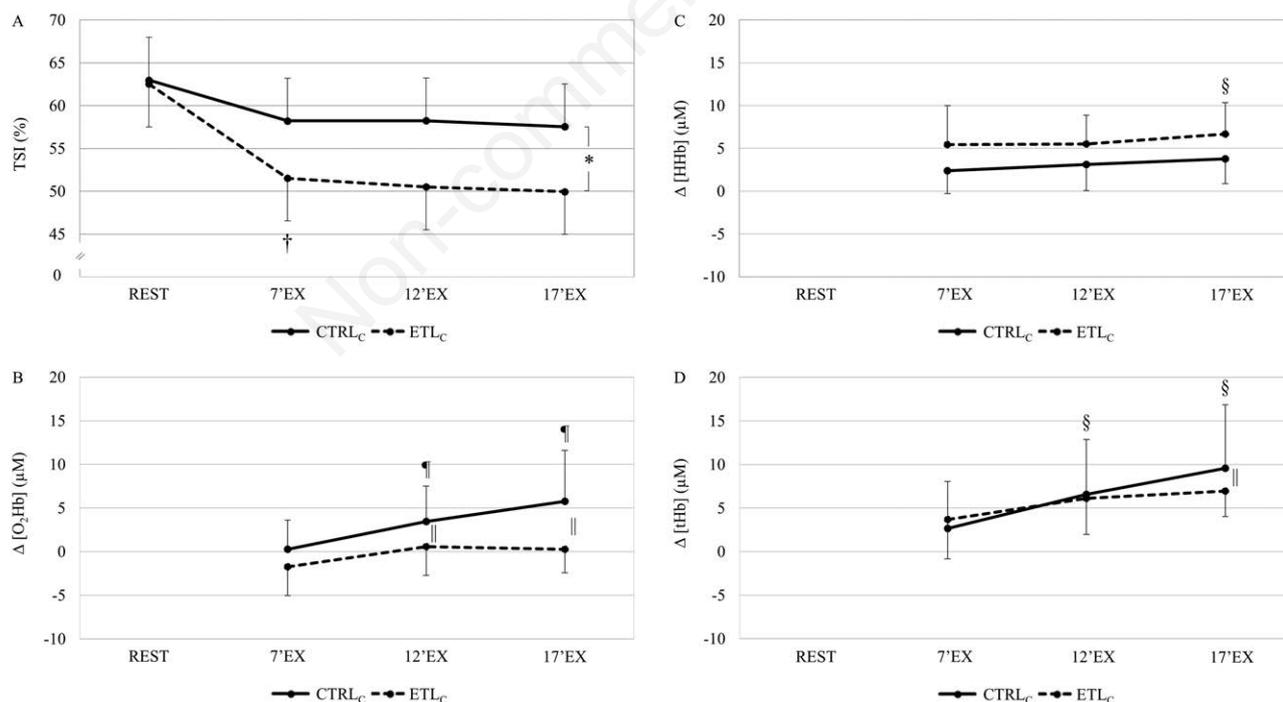
### Intercostal muscle oxygenation

In response to exercise, increase in  $[O_2Hb]$  was lower in ETL condition than in control. This may be explained by a rise in intercostal muscle oxygen consumption due to high expiratory effort. Indeed, as  $\Delta [HHb]$  tended to be higher than in control condition, greater oxygen extraction probably occurred in respiratory muscles. Otherwise, the more  $V_t/Te$  increased from rest to exercise, the more  $[O_2Hb]$  was impaired. As a rise in expiratory flow rate with ETL may suggest increased activity of respiratory muscles, greater oxygen extraction probably occurred in participants who more pronouncedly increased their  $V_t/Te$ .

In a previous study conducted in healthy subjects at rest [26], we suggested that compression of blood vessels due to vigorous breathing probably occurred in intercostal muscles when ETL was applied. As a result, the lower  $[O_2Hb]$  observed in the muscles was

likely due to the lower blood volume (*i.e.*  $[tHb]$ ). In the present study, according to changes in  $[tHb]$ , the lower  $\Delta [O_2Hb]$  in ETL condition could be explained, at least at the end of the exercise, by a limited increase in blood volume resulting from high intramuscular pressure. In agreement with our results, Vogiatzis *et al.* [30] demonstrated in patients with chronic obstructive pulmonary disease (COPD) that, when expiratory resistance was decreased at exercise by breathing a helium-enriched gas, oxygen delivery was improved in intercostal muscles. All of these results demonstrate that vascular compression may have an effect on muscle oxygenation. Lower changes in  $[O_2Hb]$  in ETL condition could likewise be due to reduced systemic arterial oxygen content, as  $SpO_2$  was lower with ETL than in control condition throughout exercise, as observed in previous studies [17,31]. One hypothesis was that with ETL, higher pulmonary pressure could lead to compression of the alveolar blood vessels, thereby impairing the ability to transfer oxygen from the lung alveoli to the pulmonary capillaries [32].

In the present study, TSI was lower in ETL condition than in control throughout exercise. This result agrees with that of Athanasopoulos *et al.* [17]. In their study, healthy subjects performed a short and maximal exercise while the expiratory flow was limited by a Starling resistor to 1 l/sec. In this context, oxygen saturation in intercostal muscles was impaired despite an increase in muscle blood flow. As TSI reflects dynamic balance between  $O_2$  supply and  $O_2$  consumption in the tissue [33], these results suggest that whatever the intensity of exercise, blood flow and/or oxygen delivery were probably insufficient to meet the metabolic needs of the respiratory muscles. Such a situation probably leads to exercise intolerance in COPD.



**Figure 3.** Intercostal muscle oxygenation in control and expiratory threshold load conditions (Ctrl<sub>c</sub> and ETL<sub>c</sub>). Values are mean  $\pm$  SD. Tissue saturation index (TSI, panel A) at rest and at the 7<sup>th</sup> (7'EX), the 12<sup>th</sup> (12'EX) and the 17<sup>th</sup> (17'EX) minute of the steady-state exercise. Concentration changes in oxyhaemoglobin ( $\Delta [O_2Hb]$ , panel B), deoxyhaemoglobin ( $\Delta [HHb]$ , panel C), and total haemoglobin ( $\Delta [tHb]$ , panel D). †different from Rest in the corresponding condition ( $p < 0.01$ ). Double bar because different from Ctrl<sub>c</sub> during exercise at the corresponding time ( $p < 0.05$ ); \*different from Ctrl<sub>c</sub> during exercise regardless of time ( $p < 0.01$ ; effect size between large and very large); †different from 7'EX in the corresponding condition ( $p < 0.05$ ); §different from 7'EX regardless of condition ( $p < 0.05$ ). Two-way repeated measures ANOVA;  $n = 12$ .

## Dynamic hyperinflation

DH refers to a rise in end-expiratory volume above the relaxation volume of the respiratory system. This shift is frequently observed in COPD patients, especially during exercise. In our study, DH was assessed according to change in IC from rest [9,24]. In ETL condition, IC was decreased at the end of the exercise, suggesting that DH appeared when exercise was lengthened. At the same time, EFL was not observed, so we can suppose that DH may allow subjects to achieve higher expiratory flows by shifting tidal breathing to higher lung volumes. Our results agree with data reported by Stark-Leyva *et al.* [34] in healthy subjects exercising with a 10-cmH<sub>2</sub>O ETL. The reduction in IC of 400 ml observed in our study was also consistent with that reported in COPD patients [5,6]. Otherwise, correlations showed that at the end of exercise, the more IC decreased from control to ETL condition, the more Vt decreased and BF increased. These results observed in healthy young subjects are consistent with ventilatory adaptations usually observed in patients with obstructive airway disease and DH [9].

## Dyspnea

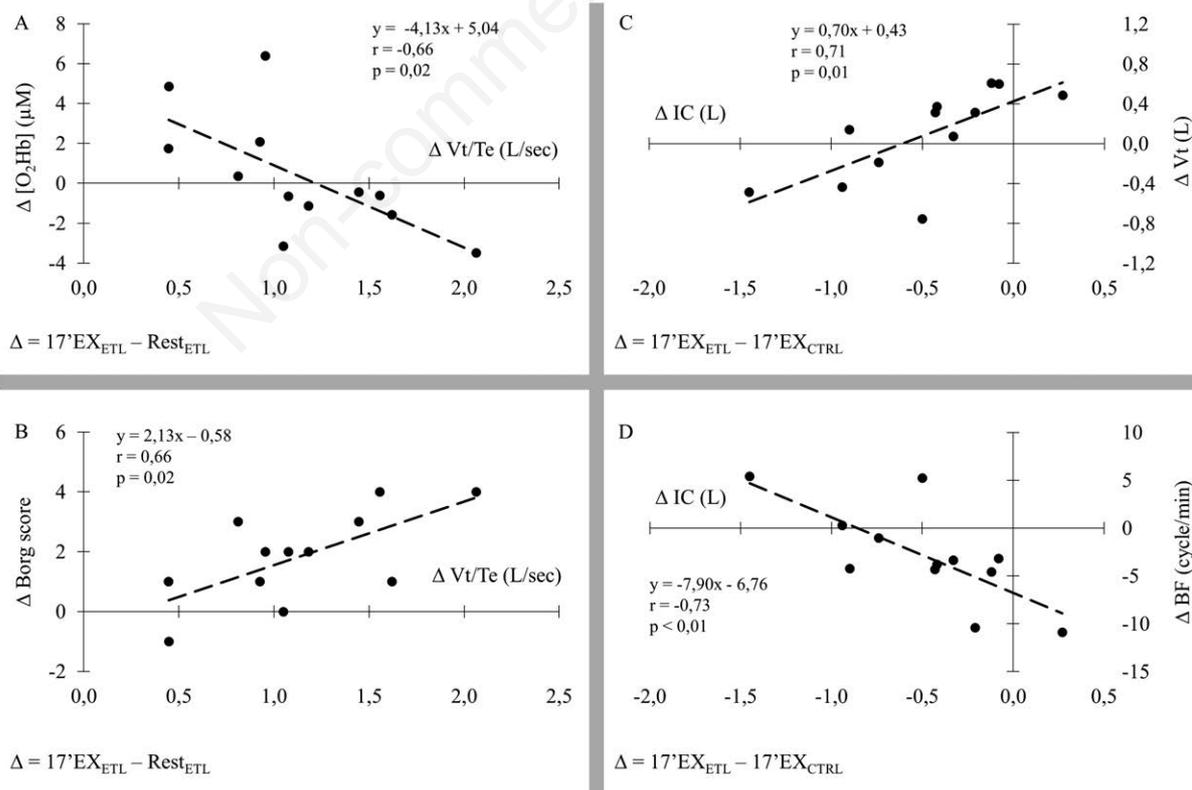
Dyspnea is frequently reported by COPD patients during exercise and is often the cause of the cessation of physical activity [10]. Dyspnea can be exacerbated by DH when it occurs during exercise because when tidal breathing is shifted to a higher lung volume, inspiratory muscle efferent is changed due to increased work of breathing. Concomitantly, the length of the respiratory muscles is modified, which disrupts the tension-length relationship of the muscle fibers and the ability of the respiratory muscles to produce strength [35,36]. Consequently, the mismatch between the inspiratory muscle efferent and the respiratory mechanical/muscular

response might exacerbate respiratory discomfort [37]. In our study, perceived dyspnea was higher in ETL than in control condition. However, dyspnea did not cause cessation of exercise and was not correlated with DH. This result is consistent with our previous study [26]. This likewise agrees with the results of Aliverti *et al.* [38] and Guenette *et al.* [39]. In their study, the authors compared dyspnea in COPD patients with and without DH during exercise and did not find difference between the groups. This confirms that DH can lead to dyspnea, but dyspnea is not exclusively induced by DH.

Besides, in the present study, we observed a correlation between dyspnea and Vt/Te, which is in agreement with the results of Kayser *et al.* [40] obtained in a similar context. Vogiatzis *et al.* [30] also demonstrated that, when expiratory muscle work was reduced in patients with COPD, dyspnea decreased. To sum up, all of these studies demonstrate that dyspnea during exercise may be induced not by only one factor, but rather by a set of causes including among which an increase in expiratory muscle load and DH.

## Study limitations

To test the effect of ETL on respiratory muscle oxygenation, intercostal muscles were chosen due to their compatibility with NIRS measurements, but their exact thicknesses were unknown. The depth of the NIRS measurement was based on theoretical external muscle thickness, 7-10 mm according to De Troyer *et al.* [41], and individual adipose tissue thickness. Nevertheless, it was not possible to specify the intercostal muscle investigated (*i.e.*, external or internal). The contribution of myoglobin to global NIRS signals is also unknown, as is the impact of changes in skin perfusion / pigmentation during exercise. However, since the participants were their own controls, it can be considered that these



**Figure 4.** Correlation between changes in oxyhaemoglobin concentration ( $\Delta [O_2Hb]$ ) and changes in expiratory flow rate ( $\Delta Vt/Te$ ). B) Correlation between changes in dyspnea ( $\Delta$  Borg score) and  $\Delta Vt/Te$ . C) Correlation between changes in inspiratory capacity ( $\Delta IC$ ) and changes in tidal volume ( $\Delta Vt$ ). D) Correlation between  $\Delta IC$  and changes in breathing frequency ( $\Delta BF$ ). Pearson correlation,  $n=12$ .

changes and their potential impact on NIRS signals were not different between the two conditions (ETL and Ctrl).

In this study, assessments of EFL and DH were based on IC measurement and on the assumptions that total lung capacity (TLC) and the ability to perform maximal inspirations were not different between the successive maneuvers. These variables were not controlled in the present study because their evaluation requires the use of invasive techniques. Furthermore, several studies have shown, in healthy subjects and in patients with obstructive lung disease, that TLC and the ability to perform deep inspirations were not disturbed during exercise [12,23,24,42-44].

The activity of the intercostal muscles was not measured electromyographically during this study. However, the recruitment of these muscles has been demonstrated at rest in healthy subjects breathing with an expiratory resistance [45]. During exercise, a more important activity of intercostal muscles was likewise demonstrated in healthy subjects during loaded breathing condition [34,46]. Physioflow device accuracy has been sometimes contested as in airway obstructive contexts [47]. In our study, this device was only used to monitor cardiac output and other cardiovascular parameters that were not the main variables of the study. Nevertheless, results agree with those of the study by Lalande *et al.* [48] in which cardiac output was measured using echo-Doppler technique.

### Strength, clinical implication and perspective of the study

This study was conducted to assess the functional and respiratory consequences of bronchial obstruction by having healthy subjects breathe against ETL during exercise. It focused on respiratory muscle oxygenation and aimed to investigate the links between muscle oxygenation, DH, EFL, and dyspnea. Consequently, the study may be of interest in diseases hallmarked by a high level of airway resistance. Furthermore, in order to assess the effect of ETL in a concrete situation, the intensity and duration of the exercise were chosen to be close to the modality recommended in patients with obstructive airway disease [49].

We demonstrated that during an exercise conducted with ETL applied at the mouth, intercostal muscle oxygenation was impaired and dyspnea increased. These deleterious effects seemed to be exacerbated when participants strongly increased their expiratory flow rate in response to exercise. Similar phenomena might occur in patients with obstructive lung disease, further impairing their already weak exercise capacities and accentuating their respiratory discomfort. As the use of positive expiratory pressure (PEP) devices is advised during exercise in COPD to prevent DH [50], alteration in respiratory muscles oxygenation must be known and taken into account by rehabilitation professionals. The counterpart of the PEP device should be studied more extensively to optimize its use or to assess the benefit risk ratio.

### Conclusion

In conclusion, this study demonstrated that intercostal muscle oxygenation was impaired when healthy subjects performed a moderate steady-state exercise with ETL. More precisely, impairment in muscle oxygenation and dyspnea were more important in participants who had the higher increases in expiratory flow rate. This study also brought out that the increase in intercostal muscle blood volume, recorded during exercise, ceased when DH occurred. Thus, altered muscle oxygenation may have been due to an insufficient increase in local blood volume to match the higher metabolic demand in ETL context. Mechanical constraints applied on muscle capillaries were probably involved.

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