Expiratory muscle loading increases intercostal muscle blood flow during leg exercise in healthy humans

Dimitris Athanasopoulos,1,2 Zafeiris Louvaris,1,2 Evgenia Cherouveim,2 Vasilis Andrianopoulos,1 Charis Roussos,1 Spyros Zakynthinos,1 and Ioannis Vogiatzis1,2

1Department of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, M. Simou, and G. P. Livanos Laboratories, and 2Department of Physical Education and Sport Sciences, National and Kapodistrian University of Athens, Athens, Greece

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ATHANASOPOULOS D, LOUVARIS Z, CHEROUVEIM E, ANDRIANOPoulos V, ROUSSOS C, ZAKYNTHINOS S, VOGIATZIS I. Expiratory muscle loading increases intercostal muscle blood flow during leg exercise in healthy humans. J Appl Physiol 109: 388–395, 2010. First published May 27, 2010; doi:10.1152/japplphysiol.01290.2009.—We investigated whether expiratory muscle loading induced by the application of expiratory flow limitation (EFL) during exercise in healthy subjects causes a reduction in quadriceps muscle blood flow in favor of the blood flow to the intercostal muscles. We hypothesized that, during exercise with EFL, quadriceps muscle blood flow would be reduced, whereas intercostal muscle blood flow would be increased compared with exercise without EFL. We initially performed an incremental exercise test on eight healthy male subjects with a Starling resistor in the expiratory line limiting expiratory flow to ~ 1 l/s to determine peak EFL exercise workload. On a different day, two constant-load exercise trials were performed in a balanced ordering sequence, during which subjects exercised with or without EFL at peak EFL exercise workload for 6 min. Intercostal (probe over the 7th intercostal space) and vastus lateralis muscle blood flow index (BFI) was calculated by near-infrared spectroscopy using indocyanine green, whereas cardiac output (CO) was measured by an impedance cardiography technique. At exercise termination, CO and stroke volume were not significantly different during exercise, with or without EFL (CO: 16.5 vs. 15.2 l/min, stroke volume: 104 vs. 107 ml/beat). Quadriceps muscle BFI during exercise with EFL (5.4 mN/s) was significantly (P = 0.043) lower compared with exercise without EFL (7.6 mN/s), whereas intercostal muscle BFI during exercise with EFL (3.5 mN/s) was significantly (P = 0.021) greater compared with that recorded during control exercise (0.4 mN/s). In conclusion, increased respiratory muscle loading during exercise in healthy humans causes an increase in blood flow to the intercostal muscles and a concomitant decrease in quadriceps muscle blood flow.

expiratory flow limitation; quadriceps muscle blood flow; near-infrared spectrometry

EXPIRATORY FLOW LIMITATION (EFL) is present in a significant proportion of patients with chronic obstructive pulmonary disease (COPD) during resting breathing, resulting in dynamic hyperinflation (20, 35). During exercise, EFL occurs in the majority of COPD patients (31), and it is associated with impaired exercise performance due to dynamic hyperinflation (5, 20, 31).

When EFL is imposed via a Starling resistor in healthy subjects during exercise, tolerance is limited by severe dyspnea sensations, abdominal pressure increases excessively during expiration, and minute ventilation (Ve) decreases, resulting in retention of CO2 (4, 6, 29). The increased work of breathing and the metabolic requirement of the respiratory muscles during exercise with EFL have been alleged to aggravate the competition for blood flow between the locomotor and the respiratory muscles. Under such circumstances, competition for blood flow could be further exacerbated by a reduction in cardiac output (CO) that has been previously documented when expiratory flow is limited during exercise in healthy subjects (6, 7).

On the other hand, experiments showed that increasing the workload of the respiratory muscles had no effect on CO, but it caused vasoconstriction in locomotor muscles, thereby compromising locomotor muscle perfusion (27, 28) in a similar manner, as it was originally shown when arm exercise was added to leg exercise, causing attenuation of blood flow in the legs (41). However, in the former experiments (27, 28), only limb and not respiratory muscle blood flow measurements were performed, and as such it is uncertain whether at a given CO respiratory muscle blood flow actually increases at the expense of blood flow to the locomotor muscles.

Measuring blood flow to the respiratory muscles is difficult owing to their anatomical arrangement, their extensive vascular network, and the large variation in muscular recruitment with varying degrees of ventilation. However, there are recent studies (25, 43, 50) succeeding in measuring changes in blood flow over the left seventh intercostal space, either during hyperpnea, or during submaximal and maximal exercise with the use of near-infrared spectroscopy (NIRS) and the light-absorbing tracer indocyanine green (ICG) dye. Blood flow measurements over the left seventh intercostal space primarily reflect the activity of the internal and external intercostal muscles (25).

Accordingly, the purpose of the present study was to investigate whether an increase in total demand for respiratory muscle blood flow induced by the induction of EFL would actually increase blood flow to the intercostal muscles and at the same time would decrease blood flow to the quadriceps muscles. To accomplish our goal, we performed simultaneous measurements of CO, as well as intercostal and vastus lateralis muscle blood flow during exercise, with and without EFL, while keeping leg muscle work constant. It was reasoned that, if intercostal muscle blood flow during exercise with EFL was greater than that recorded during exercise without EFL, while vastus lateralis muscle blood flow was reduced, this would be consistent with the notion (27, 28) that the increase of the load placed on the respiratory muscles during exercise causes an increase in blood flow to these muscles at the expense of blood flow to the locomotor muscles.
METHODS

Subjects. Eight healthy male subjects (whose physical characteristics are given in Table 1) participated in the study, which was approved by the authors’ University Hospital Ethics Committee. Before participation in the study, all subjects were informed of any risks and discomforts associated with the experiments and gave written, signed, informed consent.

Experimental design. Experiments were conducted in two visits. In visit 1, subjects underwent an incremental exercise test to the limit of tolerance by the application of a Starling resistor in the expiratory line [peak EFL exercise workload (WRpeak EFL)]. In visit 2, subjects underwent, in a balanced ordering sequence, two 6-min constant-load exercise tests at work rates corresponding to WRpeak EFL, with or without (control) the application of a Starling resistor. In more detail, consecutive patients were alternatively exercised first without flow limitation and then with flow limitation (protocol 1), or followed the opposite sequence, i.e., first exercised with flow limitation and then without flow limitation (protocol 2). Therefore, ultimately four subjects followed protocol 1 and four subjects followed protocol 2. Between tests, there was a 3-h resting period. EFL was imposed by placing a Starling resistor in the expiratory line, limiting expiratory flow to ~1 l/s. Blood flow was measured by NIRS through the assessment of the blood flow index (BFI) that was calculated from the rate of tissue ICG accumulation over time according to the Sapirstein principle (40) (see below for more details). BFI over the seventh intercostal space and over the vastus lateralis muscle was measured only during the final minute of each constant-load exercise test.

Incremental exercise test. In visit 1, the incremental exercise tests were performed on an electromagnetically braked cycle ergometer (Ergolab 800; Sensor Medics, Anaheim, CA) to establish the individual subject’s peak workload when EFL was imposed (to record WRpeak EFL) by the application of a Starling resistor. After 3 min of baseline measurements, followed by 3 min of unloaded pedaling, the work rate was increased every min by 20 W to the limit of tolerance (the point at which the work rate could not be tolerated due to severe sensation of dyspnea; see Table 1), with the subjects maintaining a pedaling frequency of 50–60 rpm. The following pulmonary gas exchange and ventilatory variables were recorded breath by breath (Ergoline 800; Sensor Medics): oxygen uptake, carbon dioxide elimination, minute ventilation, tidal volume, breathing frequency, duty cycle (inspiratory to expiratory time interval less than the time to reach peak tissue accumulation of ICG), peak minute ventilation, peak tidal volume, fpeak, peak breathing frequency, SpO2peak, percentage of arterial oxygen saturation (%SaO2), was determined using a pulse oximeter (Nonin 8600, Nonin Medical). The modified Borg scale, using a 10-point scale (9), was used to rate the magnitude of dyspnea and leg discomfort at the end of the incremental exercise test.

Constant-load exercise tests. During these tests, recording of pulmonary gas exchange and ventilatory variables was performed as mentioned above. After 3 min of baseline measurements, followed by 3 min of unloaded pedaling, the work rate was set and maintained at WRpeak EFL (i.e., the work rate achieved during the preliminary incremental test with EFL; Table 1) for 6 min in both constant-load exercise tests. CO was continuously monitored by an impedance cardiography device, while flow was measured with a hot wire pneumotachograph (Vmax 229; Sensor Medics) near the mouthpiece, and tidal volume changes were obtained by integrating the flow signal. The magnitude of dyspnea and leg discomfort was assessed every minute.

Subject preparation to measure blood flow. Subjects were prepared with a venous catheter for measurement of intercostal and quadriceps muscle blood flow. Using local anesthesia (2% lidocaine) and sterile technique, a catheter was introduced percutaneously into the right antecubital forearm vein, oriented in the proximal direction. The catheter was used to inject ICG, while it was kept patent throughout the experiment by periodic flushing with saline.

Intercostal and quadriceps muscle BFI by NIRS. To calculate intercostal and quadriceps muscle BFI, two sets of NIRS optodes were placed, one on the skin over the left seventh intercostal space, and the other over the left vastus lateralis muscle 10–12 cm above the knee, both secured using double-sided adhesive tape. NIRS signals were collected continuously during exercise.

The BFI has been calculated based on the indication that, for any time interval less than the time to reach peak tissue accumulation of tracer, the tissue receives the same fraction of the ICG bolus as quantified in arterial blood. BFI was obtained by dividing the muscle ICG concentration difference from 10 to 90% of peak height by the rise time (26, 33). A recent study demonstrated a good agreement between the NIRS ICG determined BFI and the NIRS ICG blood flow calculated by the Fick principle for both intercostal and vastus lateralis muscle groups (26, 33).

The NIRS optode separation distance was 4 cm, corresponding to a penetration depth of ~2 cm. The left intercostal space was used to avoid potential blood flow contributions from the liver on the right side of the body. Optodes were connected to a NICO 200 spectrophotometer (Hamamatsu Photonics KK, Hamamatsu, Japan), which was used to measure known volumes of ICG (range: 0.8–1.2 ml at 5 mg/ml) concentration injected into the right antecubital forearm vein, followed by a rapid 10-ml flush of isotonic saline. Tissue microcirculation ICG was detected transcutaneously by measuring light attenuation with NIRS at 775-, 813-, and 850-nm wavelengths and analyzed using an algorithm incorporating the Modified Beer-Lambert Law (21, 32, 46).

Table 1. Pulmonary function and peak exercise data with EFL

| Age, yr | 27 ± 12 |
| Height, cm | 176 ± 3 |
| Weight, kg | 77 ± 3 |
| F EV, liter | 4.1 ± 0.4 |
| FVC, liter | 4.3 ± 0.2 |
| WRpeak EFL, W | 120 ± 8 |
| VO2peak, l/min | 1.71 ± 0.06 |
| HRpeak, beats/min | 142 ± 5 |
| VIpeak, l/min | 46.2 ± 10.3 |
| VTpeak, l/min | 1.68 ± 0.40 |
| fpeak, breaths/min | 29 ± 3 |
| SpO2peak, % | 89 ± 2 |
| Borg dyspnea scores | 8 ± 1 |
| Borg leg effort scores | 6 ± 1 |

Values are means ± SE for 8 subjects. Exercise data depict the results of the incremental exercise test to the limit of tolerance by the application of a Starling resistor in the expiratory line, causing expiratory flow limitation (EFL). FEV1, force expiratory volume in 1 s; FVC, force vital capacity; WRpeak, peak work rate; VO2peak, peak oxygen uptake; HRpeak, peak heart rate; VIpeak, peak minute ventilation; VTpeak, peak tidal volume, fpeak, peak breathing frequency, SpO2peak, percentage of arterial oxygen saturation measured by pulse oximetry.
To reduce the potential influence of low arterial $O_2$ saturation from pulse oximetry ($Sp_O_2$) values on deoxy-Hb response, the following correction was applied: 
\[ [\text{deoxy-Hb}] \text{corr} = [\text{deoxy-Hb}] - [(1 - [Sp_O_2]) \times [\text{deoxy-Hb}]] \]  
(where brackets denote concentration) (10).

CO. An impedance cardiography device (Physioflow PF05L1, Manatec Biomedical, Macheren, France) was used to determine HR, stroke volume (SV), and CO at rest and during exercise. The Physioflow device uses changes in thoracic impedance in response to an administered electrical current during cardiac ejection to calculate SV. The device emits a high-frequency (75 kHz) and low-amperage (3.8 mA peak to peak) alternating electrical current via skin electrodes (13). The Physioflow device has been previously validated against the direct Fick method (8, 12, 13, 34, 36).

CO data were interpolated in 5 s for kinetic analysis (SigmaPlot 10.0, Systat Software, San Jose, CA). Since we used data from a single transition, we opt to fit CO data from 60 s of baseline pedaling to 360 s after the onset of exercise (10, 16). The model used for fitting the kinetics response of CO was the following monoexponential equation: 
\[ Y(t) = Y_b + A_p \times e^{-(t - T D)/T D_p}, \]  
where [\( Y(t) \)] is the variable under analysis, the subscripts b and p are baseline unloaded cycling and primary component, respectively; A is amplitude, TD is the time delay, TD is time constant of the exponential response of interest, and t is time. In the analysis, the TDp was taken as zero, because there is no time delay in CO (10, 16).

Statistical analysis. All data are reported as means ± SE, unless otherwise stated. SE was used rather than SD, because our interest is in mean differences between the two constant-load exercise tests rather than in differences between subjects. Two-way ANOVA with repeated measures was used to identify statistically significant differences across different time points during exercise between the two constant-load exercise tests for CO, HR, SV, as well as intercostal and quadriceps muscle tissue $O_2$ saturation, deoxygenated Hb (deoxy-Hb), and all pulmonary gas exchange variables. One-way ANOVA with repeated measures was used to identify statistically significant differences across the mean values within each constant-load exercise test for all of the aforementioned variables. When one- or two-way ANOVA detected statistical significance, pairwise differences were identified using Tukey’s honestly significant difference post hoc procedure. Comparisons for the blood flow indexes for quadriceps and intercostal muscles (calculated only during the final minute of exercise) between control and EFL constant-load trials were made by paired t-tests. The level of significance for all of the above analyses was set at $P < 0.05$.

RESULTS

Hemodynamic responses. CO during quiet breathing, unloaded cycling, and exercise, with and without EFL, is shown in Fig. 1A. During both constant-load exercise tests, CO increased linearly up to the third minute of exercise and leveled off thereafter. During exercise with expiratory muscle loading, CO tended to be greater compared with control ($P = 0.088$) (Fig. 1A). In addition, flow limitation was associated with slower ($P = 0.032$) on-exercise CO kinetics compared with control exercise (mean time constant 93 ± 9 compared with 68 ± 4 s). Furthermore, HR was significantly greater ($P = 0.022$) during flow-limited exercise compared with control.

Ventilatory responses and sensations of dyspnea and leg discomfort. $V_E$, %$Sp_O_2$, end-tidal carbon dioxide, and sensations of dyspnea and leg discomfort during rest, unloaded cycling (UNL), and exercise, with and without EFL, are shown in Fig. 1. During control exercise, $V_E$ increased linearly up to the second minute of exercise and leveled off thereafter (Fig. 1D), while, during exercise with EFL, $V_E$ increased up to the first minute of exercise and then exhibited a plateau. $V_E$ was significantly lower ($P = 0.022$) during flow-limited exercise. The lower $V_E$ during exercise with EFL resulted in a significantly higher ($P = 0.001$) end-tidal carbon dioxide (Fig. 1E) and significantly lower ($P = 0.005$) %$Sp_O_2$ (Fig. 1B). Duty cycle was significantly shorter ($P = 0.001$) during exercise with EFL. Sensations of dyspnea (Fig. 1C) and leg discomfort (Fig. 1F) during exercise with EFL were significantly greater ($P = 0.003$ and 0.045, respectively) compared with control exercise.

Intercostal and quadriceps muscle oxygenation by NIRS. Figure 3 displays changes from baseline (i.e., quiet breathing) for intercostal and quadriceps muscle oxygen saturation and deoxygenated hemoglobin during unloaded cycling and exercise, with and without EFL. During control exercise, intercostal muscle oxygen saturation (Fig. 3A) and deoxygenated hemoglobin (Fig. 3B) remained unchanged compared with baseline, whereas, during exercise with EFL, intercostal muscle oxygen saturation (Fig. 3A) significantly decreased and intercostal muscle deoxygenated hemoglobin (Fig. 3B) significantly increased. Hence, intercostal muscle oxygen saturation and deoxygenated hemoglobin were significantly different ($P = 0.037$ and 0.017, respectively) between the two constant-load exercise tests (Fig. 3, A and B).

During control exercise, quadriceps muscle oxygen saturation (Fig. 3C) and deoxygenated hemoglobin (Fig. 3D) remained unchanged compared with baseline throughout the test. In contrast, during exercise with EFL, quadriceps muscle oxygen saturation (Fig. 3C) significantly decreased from baseline, while quadriceps deoxygenated hemoglobin (Fig. 3D) exhibited a tendency to increase ($P = 0.074$). Quadriceps muscle oxygen saturation and deoxygenated hemoglobin were significantly different ($P = 0.017$ and 0.038, respectively) between the two constant-load exercise tests (Fig. 3, C and D).

DISCUSSION

The present study investigated whether, during exercise, an increase in respiratory muscle loading induced by EFL decreases blood flow to the quadriceps muscles, while at the same time it increases blood flow to the intercostal muscles. Simultaneous measurements of intercostal and vastus lateralis muscle blood flow indexes using NIRS and the light-absorbing tracer ICG dye were performed during exercise, with and without EFL, while keeping leg muscle work constant. The novel finding of the present study is that, during exercise with EFL, directly measured intercostal muscle blood flow was greater and quadriceps muscle blood flow was lower compared with exercise without EFL. Therefore, it is suggested that EFL most likely causes redistribution of blood flow from the locomotor to the respiratory muscles.
EFL as a model of expiratory muscle loading. The experimental model used in this study has been shown to induce intolerable dyspnea sensations, CO₂ retention, impaired exercise performance, excessive expiratory muscle recruitment, reduced duty cycle, and decreased SaO₂ (6) in healthy subjects. In addition, previous studies by Aliverti and colleagues (4, 6, 29) have shown that the major effect of EFL is that it slows expiratory flow and increases inspiratory flow. Thus EFL imposes a load that decreases the shortening velocity of expiratory muscles and at the same time increases the shortening velocity of inspiratory muscles. The result is that the power output of the rib cage muscles, the diaphragm, and the expiratory abdominal muscles is increased up to fourfold during flow-limited compared with control exercise, thereby indicating an increase in central drive to all respiratory muscles (4, 29). In the present study, we did not assess the power of the respiratory muscles, albeit we reported that flow limitation, as in previous studies (4, 6, 29), led to hypoxemia (Fig. 1B), hypercapnia (Fig. 1E), decreased duty cycle, and V̇E (Fig. 1D), whereas all subjects experienced intolerable dyspnea sensations (Fig. 1C).

Fig. 1. Effect of flow limitation on breathing pattern. Cardiac output (A), percentage of oxygen saturation (B), sensations of dyspnea (C), minute ventilation (D), end-tidal carbon dioxide (E), and sensations of leg discomfort (F) are shown during quiet breathing (QB), unloaded cycling (UNL), and exercise with expiratory flow limitation (EFL: ●) and without EFL (control: ○). Values are means ± SE for 8 subjects. Significant differences †between the two conditions, and *compared with 6th min of exercise: P < 0.05.
Blood flow redistribution. High-intensity whole body exercise is known to induce expiratory muscle fatigue (45, 47). During exercise with flow limitation, measurements of esophageal and gastric pressures have revealed that strong inspiratory and expiratory muscle recruitment takes place (3). Hence, it is likely that persistent expiratory muscle recruitment taking place during the flow-limited exercise trials in the present study led to expiratory muscle fatigue. Fatigue of the respiratory muscles would be expected to activate the so-called respiratory muscle metaboreflex, thereby leading to locomotor muscle vasoconstriction and to a decrease in limb blood flow (18, 19). Interestingly, in the present study, we observed a reduction in quadriceps muscle BFI compared with control exercise when EFL was imposed (Fig. 2). This reduction in blood flow to the locomotor muscles could potentially serve to increase blood flow to the respiratory muscles (18, 19). In fact, we were also able to demonstrate a significant increase in intercostal muscle blood flow during exercise with EFL compared with control (Fig. 2).

Blood flow measurements over the left seventh intercostal space typically reflect the activity of the internal and external intercostal muscles: the former being expiratory and the latter inspiratory muscles (25). Hence, given that, during exercise with EFL, all respiratory muscles typically increase their power output up to fourfold (4, 29), the finding that blood flow to the intercostal muscles increased during exercise with EFL compared with control exercise (Fig. 2) could be attributed to the increased load imposed on both internal and external intercostal muscles. It is likely that, during exercise with EFL, blood flow was preferentially devoted to the respiratory muscles as their metabolic demand was increased, while the demand of the locomotor muscles remained unchanged. This finding is consistent with previous suggestions that, during exercise, the increased load placed on the respiratory muscles causes redistribution of blood flow from the locomotor to the respiratory muscles (27, 28).

Was the decrease in leg matched by the increase in intercostal muscle blood flow? Based on a recently published study showing good agreement between the NIRS ICG determined BFI and the NIRS ICG blood flow calculated by the Fick principle for both intercostal and vastus lateralis muscle groups (26), we estimated that, compared with control exercise, mean intercostal muscle blood flow during EFL exercise would increase from 15 to 20 ml·kg$^{-1}$·100 g$^{-1}$, respectively (i.e., 33% increase), whereas vastus lateralis mean muscle blood flow would be reduced from 38 to 34 ml·min$^{-1}$·100 g$^{-1}$, respectively (i.e., 10% decrease). These values are in agreement with those recently reported by our group (50) in healthy individuals during cycling at 120 W. Considering that, in healthy trained individuals exhibiting similar anthropometric characteristics to those of the subjects in the present study (13), two-leg blood flow during exercise at 120 W requires 60–70% of CO (13), then, in our control experiments, two-leg blood flow is estimated to be in the range of 10 l/min as CO was ~15 l/min. When EFL was imposed, quadriceps muscle blood flow was reduced by 10%, and hence leg blood flow by ~1.0 l/min. This figure is in agreement with that (0.9 l/min) reported by Harms et al. (27) when respiratory muscle load was imposed in healthy subjects. Similarly, considering that respiratory muscle blood flow requires 10–15% of CO during submaximal exercise (1), then it is estimated that respiratory muscle blood flow in our experiments would be in the range of 2.0 l/min. Since intercostal muscle blood flow increased by 33% by the application of EFL, this change would correspond to an increase of ~0.75 l/min. As the mass of the intercostal muscles corresponds only to one-third of the total respiratory musculature (37, 39), the estimated decrease in leg blood flow (by 1.0 l/min) cannot be fully accounted for by the increase in blood flow to the intercostal muscles (i.e., 0.75 l/min is equivalent to 0.25 l/min). It is, therefore, likely that a significant proportion of blood flow increase was distributed to other respiratory muscles, such as the diaphragm and especially the expiratory abdominal muscles whose power has been shown to increase by two- to fourfold during flow-limited exercise (4, 6, 29, 45).

Intercostal and quadriceps muscle oxygenation by NIRS. Intercostal muscle oxygen saturation (Fig. 3A) and deoxygenated hemoglobin (Fig. 3B) [the latter a proxy of tissue fractional oxygen extraction (17, 22–24)] did not change during control exercise, thus suggesting that the oxygen demand of the intercostal muscles was met by the available blood flow and oxygen delivery. In contrast, intercostal muscle oxygen saturation declined and deoxygenated hemoglobin increased during
exercise with EFL. This finding suggests that, despite the increased blood flow (Fig. 2), the oxygen demand of the intercostal muscles was not sufficiently met by the available oxygen delivery, and the increased tissue fractional oxygen extraction increased. Therefore, it seems likely that the increase in blood flow to the intercostal muscles during EFL exercise was insufficient to offset the reduced SaO₂ (Fig. 1B) and to meet the increased oxygen demand, and, as such, intercostal muscle oxygen saturation decreased, whereas deoxygenated hemoglobin increased (Fig. 3, A and B). Furthermore, these findings infer a mismatch between oxygen delivery to, and demand of, the intercostal muscles, thereby indicating that limited respiratory muscle oxygen delivery may have contributed to the development of expiratory muscle fatigue. In addition, during exercise with EFL quadriceps muscle, blood flow was reduced compared with control exercise (Fig. 2). This reduction is most likely responsible for the decline in quadriceps muscle oxygen saturation and the increase in deoxygenated hemoglobin during exercise with EFL compared with control exercise (Fig. 3, C and D) and could, in part, justify the greater degree of leg discomfort experienced by the subjects (Fig. 1F).

There are studies reporting the effects of either the resistive breathing or respiratory muscle unloading on leg muscle oxygenation during exercise (10, 16, 32). It has been documented that respiratory muscle unloading, via a proportional-assist ventilator, increased oxygen availability to the lower limbs during constant-load exercise in patients with advanced COPD (10). As these changes were not related to increased systemic oxygen delivery, it was suggested that a fraction of CO was redistributed from the respiratory to the locomotor muscles as a consequence of proportional-assist, ventilator-induced reductions in respiratory muscle load and blood flow requirement. In fact, the study by Borghi-Silva et al. (10) confirmed earlier suggestions by Simon et al. (42) that, in some patients with COPD, peripheral muscle blood flow and oxygen delivery to the locomotor muscles are limited.

**Hemodynamic responses.** Although previous studies have documented that expiratory loading during exercise significantly reduces CO (6, 30, 38, 44), CO during exercise with
expiratory muscle loading in the present study tended to be greater compared with control, whereas on-exercise kinetic CO responses were significantly slower compared with control. Collectively, these findings could be attributed to the increased metabolic demand by the respiratory muscles, whose oxygen cost of breathing during flow limitation may exceed 15% of total whole body energy requirement (1). Slowing down of on-exercise CO kinetics may thus be interpreted as a delay in central hemodynamic response to reach a steady state, which often happens when muscle energy demand is not sufficiently matched by the increase in VO2 (10, 16). As our own study (25) has shown a linear increase in CO relative to the work of breathing across different levels of VE during resting hyperpnea, it is conceivable that increased respiratory muscle power induced by flow limitation in the present study induced an increase in CO.

Study limitations. Blood flow measurements of the main expiratory muscles, i.e., the abdominal muscles, were not performed. Placing the NIRS optodes on the abdominal muscles may result in an underestimation of blood flow measurements, owing to a potential contribution of skin and subcutaneous tissue to the light-absorption signal. However, blood flow measurements over the left seventh intercostal space primarily reflect the activity of the internal and external intercostal muscles, which develop the necessary pressure to move the rib cage (2). In fact, a recent study (25) revealed that intercostal muscle blood flow assessed by the NIRS-ICG technique during isocapnic hyperpnea in healthy individuals would primarily reflect blood flow perfusing the inspiratory, but also the expiratory, intercostal muscles (25). In addition, the intercostal muscles are easily accessible and are active across a wide range of ventilation, whereas studies have shown a linear relationship between intercostal muscle electromyographic activity and the work of breathing (48). Nevertheless, lack of actual measurements of work of breathing and calculations of the power output of the rib cage muscles, the diaphragm, and the expiratory abdominal muscles constitutes a limitation, as we are unable to provide evidence of an increase in central drive to those respiratory muscles.

Another possible limitation of the present study might be the calculation of the BFI for both respiratory and locomotor muscles instead of actual measurements of blood flow by NIRS using ICG. Actual measurements of blood flow, expressed in milliliters per minute per 100 grams, need the determination of CO by the dye dilution method and the Fick principle, which requires the subject to have an arterial catheter in place (49, 50). Nevertheless, the NIRS ICG determined BFI has recently been validated by Habazettl et al. (26) and has been shown to have good agreement with the NIRS ICG blood flow calculated by the Fick principle for both intercostal and vastus lateralis muscle groups. In addition, although the measurement of CO has been validated against the direct Fick method (15), this method has not been validated while restricting expiration. However, in patients with COPD exhibiting EFL during exercise, the Physio-Flow device has been shown to overestimate measurements of CO compared with the Fick method, both at rest and during exercise (12), and, although a fair correlation is observed between those methods, the accuracy of the measurement may be questioned.

Conclusion. Increased respiratory muscle loading induced by EFL during exercise in healthy humans causes an increase in blood flow to the intercostal muscles and a concomitant decrease in quadriceps muscle blood flow.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

INTERCOSTAL MUSCLE BLOOD FLOW ELEVATION DURING EXERCISE


