Blood shifts between body compartments during submaximal exercise with induced expiratory flow limitation in healthy humans

Running Title: Blood shifts during exercise with induced expiratory flow limitation

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Key points summary

- External expiratory flow limitation (EFLe) can be applied in healthy subjects to mimic the effects of chronic obstructive pulmonary disease (COPD) and safely study the mechanisms of exercise intolerance associated with the disease.
- At maximal exercise intensity with EFLe, exercise intolerance results from high expiratory pressures altering the respiratory pump mechanism and limiting venous return.
- We used double body plethysmography to quantify blood shifting between the trunk and the extremities and examine whether the same effects occur with EFLe at submaximal exercise intensity, where the increase in expiratory pressures is milder.
- Our data show that during submaximal exercise, EFLe amplifies the respiratory pump mechanism, each breath producing greater blood displacements between the trunk and the extremities, with a prevailing effect from lower inspiratory intra-thoracic pressure progressively drawing blood into the trunk.
- These results help better understand the hemodynamic effects of respiratory pressures during submaximal exercise with expiratory flow restriction.

ABSTRACT

External expiratory flow limitation (EFLe) can be applied in healthy subjects to mimic the effects of COPD during exercise. At maximal exercise intensity, EFLe leads to exercise intolerance due to respiratory pump dysfunction limiting venous return. We quantified blood shifts between body compartments to determine whether such effects can be observed during submaximal exercise, when the load on the respiratory system is milder. Ten healthy men (25.2±3.2 y, 177.3±5.4 cm, 67.4±5.8 kg) exercised at 100 W (~40 %$\dot{V}O_2$max) while breathing spontaneously (CTRL) or with EFLe. We measured respiratory dynamics with optoelectronic plethysmography, esophageal (Pes) and gastric (Pga) pressures with balloon catheters, and blood shifting between body compartments with double body plethysmography. During exercise, EFLe resulted in (1) greater intra-breath blood shifts between the trunk and the extremities (518±221 (EFLe) vs 224±60 ml (CTRL); P<0.001) associated with lower Pes during inspiration (r=0.53, P<0.001) and higher Pga during expiration (r=0.29, P<0.024) and (2) a progressive pooling of blood into the trunk over time (~700 ml after 3 min exercise; P<0.05), explained by a predominant effect of lower inspiratory Pes (r=0.54; P<0.001) over that of increased Pga. It follows that during submaximal exercise, EFLe amplifies the respiratory pump mechanism, with a prevailing contribution from lower inspiratory Pes over increased expiratory Pga, drawing blood into the trunk. Whether these results can be replicated in COPD patients remains to be determined.

INTRODUCTION

Exercise intolerance is a pervasive feature of chronic obstructive pulmonary disease (COPD), yet a comprehensive understanding of the underlying mechanisms is still lacking (Aliverti *et al.*, 2008; O'Donnell *et al.*, 2019). To provide further insights, a series of investigations limited expiratory flow in healthy persons by introducing a Starling resistor into the expiratory line ('external expiratory flow limitation'; EFLe), thus mimicking some of the functional restrictions observed in patients with COPD (Kayser *et al.*, 1997; Aliverti *et al.*, 2002; Iandelli *et al.*, 2002). Because of its transitory nature when imposed in healthy persons, EFLe allows exercising at maximal intensity without risk, while simulating several of the pathophysiological abnormalities observed in patients. From these experiments, it was proposed that the decline in exercise tolerance observed with EFLe stems from a dysfunction of the respiratory pump mechanism (Aliverti *et al.*, 2007). Specifically, the development of high expiratory pressures resulting from EFLe would interfere with venous return by narrowing the pressure gradient between the peripheral and central circulation, as proposed earlier for patients with COPD (Potter *et al.*, 1971). In support of this contention, respiratory maneuvers increasing intra-abdominal pressure during expiration can result in a temporary halting of venous return from the extremities (Miller *et al.*, 2005*a*, 2005*b*). Accordingly, a drop in cardiac output was observed when switching from normal breathing to EFLe during constant-load maximal exercise (Aliverti *et al.*, 2005). Furthermore, it was estimated that EFLe can result in blood displacements from the trunk to the extremities during maximal intensity exercise (Iandelli *et al.*, 2002). It was then speculated that these circulatory impediments would set in motion a vicious circle decreasing pulmonary vascular blood volume, increasing ventilatory dead space and exacerbating hypercapnia, which would ultimately lead to further the recruitment of expiratory muscles, and so forth (Aliverti *et al.*, 2007). Because EFLe and expiratory loading in general is accompanied by greater intra-thoracic pressure swings, cardiac function is also impacted (Stark-Leyva *et al.*, 2004; Cheyne *et al.*, 2020).

The use of EFLe in previous studies allowed gathering valuable information about the potential mechanisms limiting maximal exercise capacity in patients with expiratory flow restriction such as in COPD. However, in practice, patients with COPD rarely venture into such high intensities by fear of overloading their respiratory system, since unlike healthy individuals experiencing EFLe, they cannot escape from their condition (Macklem, 2005). Therefore, determining whether the dysfunction of the respiratory pump observed during maximal exercise is also present at lower exercise intensities is of relevance, since a lower metabolic load would be expected to cause less pronounced increases in expiratory pressure. In the present study, we aimed to address this issue by carrying out an assessment of the respiratory and blood shifting responses to EFLe during

submaximal exercise in healthy subjects. Specifically, we aimed to (1) determine the impact of EFLe on blood displacements between body compartments during submaximal exercise, and (2) identify the relationship between these blood displacements and the dynamics of respiratory pressures.

METHODS

Ethical approval

This study was carried out in accordance with the 2013 version of the *Declaration of Helsinki* and was approved by the local institutional review board (CER-VD, protocol ID: 2016-00860). Ten healthy men took part in the experiments and gave written informed consent prior to data collection. Their anthropometric parameters are shown in **Table 1**.

Experimental procedure

The experimental setup is represented in **Figure 1**. Participants sat in a whole-body plethysmography cabin and performed sequences of constant-load submaximal cycling exercise (100 W) for 3 minutes with EFLe or breathing spontaneously without restriction (CTRL). They wore a nose clip and breathed room air through a mouthpiece connected to a tube across the cabin's front wall. EFLe was implemented using a Starling resistor mounted on the expiratory end of a two-way non-rebreathing valve (Hans Rudolph, Inc., Shawnee, KS, USA) and restricting expiratory flow to 1 $L \cdot s^{-1}$. Each exercise sequence was repeated three times per condition in a randomized order and was preceded by a 1-min resting period and followed by two minutes of recovery. Between each sequence, the door of the cabin was opened to allow restoration of baseline thermodynamic conditions, monitored with a digital transducer (DHT22, Aosong, Guangzhou, China). To mitigate the rise in temperature and humidity during each exercise sequence, the cabin was equipped with a conditioning system consisting of eight Peltier cells combined with a set of fans.

Exercise was performed on a custom-built cycle ergometer designed to allow pedaling in the confined space of the cabin. The fixed resistance provided by the friction of a belt on the flywheel elicited a power output of 100 W at a fixed cadence of 90 rpm. Power output was measured by wireless power meter pedals (PowerTap P1, SRAM LLC, Chicago, IL, USA) and participants were guided by a metronome beating at 90 bpm.

On a separate day, participants performed a ramp incremental test on a cycle ergometer (Excalibur Sport, Lode B.V., Groningen, The Netherlands) to determine maximal oxygen uptake ($\dot{V}O_2max$). After 5 minutes of warm up at 1 $W \cdot kg^{-1}$, power output was

gradually increased at a rate of 1 $W \cdot 2s^{-1}$ until participants reached exhaustion. A calibrated metabolic cart (MedGraphics CPX/D, Medical Graphics Corp., St Paul, MN, USA) monitored oxygen uptake ($\dot{V}O_2$) and $\dot{V}O_2$max was defined as the highest $\dot{V}O_2$ value reached after averaging breath-by-breath data by 15-s intervals.

Starling resistor

The custom-built Starling resistor consisted of a collapsible rubber tube enclosed in a rigid plastic chamber. During the EFLe runs, the mouthpiece through which participants breathed was connected to the rubber tube as well as to a second opening directly connected to the rigid cylinder. Mouth pressure was thus relayed to the chamber, compressing the tube. The size of the second opening was adjusted to render expiratory flow independent of pressure at 1 $L \cdot s^{-1}$ similarly to previous experiments (Aliverti *et al.*, 2002; Iandelli *et al.*, 2002). Participants were connected to the Starling resistor upon closing the door and then throughout the entire exercise sequence, including the resting and recovery periods.

Measurements

During each sequence, a pneumotach mounted on an opening at the top of the cabin measured airflow in and out of the plethysmograph to monitor changes in total body volume (ΔVb) by offline mathematical integration of the flow signal. The gas analyzer provided continuous analogue signals of airflow and oxygen fraction (FO_2) at the mouth (MedGraphics CPX/D, Medical Graphics Corp., St Paul, MN, USA). Eight infrared cameras placed around the cabin tracked the three-dimensional positions of 89 retro-reflective markers taped onto the participant's trunk to monitor chest wall volume (Vcw) with a 3D calibrated motion analyzer (OEP, BTS Bioengineering, Milan, Italy). Two pressure transducers (RCEM250DB, Sensortechnics, Puchheim, Germany), calibrated with a water manometer, measured changes in esophageal (Pes) and gastric pressure (Pga) from balloon-tipped catheters (47-9005, Cooper Surgical, Trumbull, CT USA) introduced nasally and placed in the esophagus and stomach, respectively. Correct positioning of the balloons was verified by visual inspection of the pressure values during quiet breathing, sniffing and breathing at higher tidal volume. Esophageal and gastric balloons were inflated with 1 and 1.5 ml of air, respectively, as recommended by the manufacturer. All signals converged into an analogue to digital data acquisition system embedded into the OEP device and were resampled at 60 Hz and time-aligned for analysis.

Computation of blood shifts (Vbs)

∆Vb and variations in Vcw (∆Vcw) were collected simultaneously. ∆Vb are due to both changes in lung volumes and gas compression and decompression in the lungs, while ∆Vcw depend on the same factors in addition to blood coming in and going out of the trunk. Mathematical subtraction of the two signals yielded the volume of blood shifted between the trunk and the extremities (volume of blood shift; Vbs) (Aliverti *et al.*, 2009, 2010; Uva *et al.*, 2016; LoMauro & Aliverti, 2018; Stucky *et al.*, 2021). Prior to the computation of Vbs, a validated algorithm was used to (1) correct the drift in the ∆Vb signal due to changes in thermodynamic conditions based on measured values of temperature and humidity and (2) automatically select the level of a wavelet filter applied to remove the remaining drift in ∆Vb due to numerical integration of the flow signal (Stucky *et al.*, 2020).

Absolute lung volume (VL)

Breath-by-breath absolute lung volume (VL) could not be estimated directly from the Vcw signal, because the latter also comprises non-gas volume, the volume of gas compressed in the lung, and blood shifts between the trunk and the extremities. Instead, we estimated changes in VL from mathematical integration of airflow measured at the mouth (Vm) and used Vcw to correct the signal for integrator drift and estimate VL. We first determined the non-gas portion of Vcw as the difference between end-expiratory Vcw and the functional residual capacity (FRC) calculated for each subject from height and age (Quanjer *et al.*, 1993), and subtracted this value from Vcw. Assuming that gas compression and Vbs are nil at end-inspiration, we then set the first end-inspiratory Vm value equal to the corresponding end-inspiratory Vcw value corrected for non-gas volume. Each following end-inspiratory Vm value was then adjusted so that the slope between two successive end-inspiratory Vm values would be equal to the slope between two successive end-inspiratory Vcw values corrected for non-gas volume.

From the computation of VL and the measurement of FO_2 at the mouth, we computed breath-by-breath $\dot{V}O_2$ at the mouth and corrected this value for changes in lung O_2 stores to better approximate alveolar oxygen uptake (Auchincloss *et al.*, 1966; Aliverti *et al.*, 2004*a*).

Data analysis

From the VL signal, we identified end-inspiratory and end-expiratory points and derived respiratory rate (RR) and tidal volume (Vt). The former was calculated as 60 divided by the duration of each breath in seconds while the latter was taken as the amplitude between adjacent minimum and maximum VL values. The product of Vt and RR yielded total minute ventilation ($\dot{V}E$). Inspiratory (Tinsp) and expiratory time (Texp), as well as duty cycle (the ratio between inspiratory time and total breath time) were computed for each breath. The transdiaphragmatic pressure (Pdi) signal was obtained by offline subtraction of Pes from Pga.

To follow the dynamics of the respiratory and hemodynamic variables, each experimental run was divided into six slots of 60 seconds (Rest, Ex1, Ex2, Ex3, Rec1, Rec2), over which Vt, RR, $\dot{V}E$, Texp, Tinsp, duty cycle and $\dot{V}O_2$ signals were averaged. For VL and Vcw, end-expiratory and end-inspiratory points were averaged separately within each 60-s period, while peak expiratory and peak inspiratory values were used for Pes, Pga, Pdi and Vbs. Intra-breath maximal variations of Pes, Pga and Vbs were computed breath-by-breath and averaged over each 60 seconds time slot.

To assess the association between respiratory mechanics and blood displacements during exercise, we computed a series of correlation analyses between inspiratory and expiratory pressures and Vbs. We evaluated these interactions at two different levels: a) the changes in 'operational' Vbs (Vbs,OP) relative to the longer-term variations over the whole exercise sequence compared to quiet breathing and b) the intra-breath Vbs variations (Vbs,I-B). First, breath-by-breath Pes, Pga and Vbs signals were ensemble averaged over the last minute of exercise (Ex3) to create typical traces over a single breath. The averaging boundaries were defined as the end-inspiratory and end-expiratory points determined from the VL signal. Then, Vbs,I-B was obtained by subtracting the end-expiratory Vbs value from the whole ensemble-averaged Vbs signal. The same operation was performed for Pga to obtain abdominal pressure (Pab). All signals were then averaged separately during inspiration and expiration. Pearson's correlation coefficients for the relationships *Pes vs Vbs,OP* and *Pga vs Vbs,OP* were computed separately for the inspiratory and expiratory phases to assess the effect of pressure on changes in operational Vbs. The same operations were performed for *Pes vs Vbs,I-B* and *Pab vs Vbs,I-B* to examine intra-breath associations.

Statistical analysis

All parameters were compared across conditions (CTRL, EFLe) and time (Rest, Ex1, Ex2, Ex3, Rec1, Rec2) using a two-way repeated measures ANOVA. All pairwise *post hoc* comparisons were performed with the Bonferroni correction. All data are reported as mean±SD. The significance level was set at 0.05. Statistical analyses were performed using SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA). Association between the normalized respiratory pressure parameters (Pes, Pga, Pab vs Vbs,OP and Vbs,I-B) over Ex3 were assessed by computing Pearson's correlation coefficients and P-values using GraphPad Prism (Prism 9.0, GraphPad Software, San Diego, CA, USA). Correlation parameters were calculated for EFLe, CTRL and for EFLe and CTRL points taken altogether. For each sequence, the first and last measured values of the temperature and humidity signals were isolated and compared using a paired t-test.

RESULTS

Numerical results and P-values for all statistical tests are reported in **Table 2**

Thermodynamic conditions

On average, during the exercise sequences, the temperature inside the plethysmograph rose from 23.6±0.8 to 24.4±1.0 °C (P<0.0001), while humidity increased from 56.2±13.1 to 80.6±18.1 % (P<0.0001).

Respiratory dynamics

Changes in Vt, RR and $\dot{V}E$ over time are shown in **Figure 2**. In both conditions, RR, Vt and $\dot{V}E$ increased progressively during exercise and decreased upon recovery. In all phases, RR was decreased with EFLe compared to CTRL. Despite a concurrent increase in Vt, $\dot{V}E$ remained significantly lower with EFLe at rest and during exercise, while it was not significantly different from the CTRL runs during recovery, as it dropped more during this phase in CTRL.

Figure 3 shows results from the temporal analysis of the respiratory cycle. In CTRL, Tinsp and Texp progressively decreased throughout exercise and were gradually restored towards baseline values upon recovery. Duty cycle followed the opposite pattern with an increase during exercise and a gradual restoration during recovery. In EFLe, while the decrease with exercise was also observed, the restoration of baseline values was more gradual becoming manifest only during the second

minute of recovery. Duty cycle decreased during exercise and continued decreasing during recovery. Texp and Tinsp were both prolonged with EFLe in all phases compared to CTRL, with a greater effect on Texp, as indicated by the systematically lower duty cycle values.

Analysis of absolute VL showed that end-inspiratory values increased throughout exercise in both conditions (**Figure 4**), with substantially greater values with EFLe compared to CTRL in all phases. End-expiratory lung volume (EELV) values were systematically higher with EFLe in all phases. On average, EELV progressively decreased with exercise in CTRL, while with EFLe they progressively increased, though the dynamics of EELV with EFLe followed a wide range of patterns.

Respiratory pressures

Results of the analysis of respiratory pressures are show in **Figure 5**. In both conditions, peak inspiratory Pes values gradually decreased with exercise while peak expiratory values gradually increased. Both were progressively restored to baseline during recovery. In all phases, EFLe resulted in lower peak inspiratory values and higher peak expiratory values compared to CTRL, which produced a systematic increase in the amplitude of intra-breath Pes swings. Peak inspiratory Pga remained stable throughout the sequence in both conditions and was elevated with EFLe during exercise and the first minute of recovery. Peak expiratory Pga increased with exercise in both conditions, with values significantly higher with EFLe in all phases. This resulted in greater intra-breath Pga swings with EFLe compared to CTRL. Pes data from one subject had to be excluded due to aberrant results (positive Pes throughout the respiratory cycle) presumably resulting from the displacement of the esophageal balloon catheter into the stomach.

Blood shifts

During CTRL, Vbs remained stable throughout the sequence. With EFLe, Vbs decreased upon initiation of exercise – indicating a shift towards the trunk – and further decreased throughout the 3 minutes of pedaling, reaching significantly lower values compared to CTRL in all stages of exercise (**Figure 6**). This effect was partly reversed during recovery with a progressive, though incomplete return to baseline values towards the end of the sequence, values remaining significantly lower compared to CTRL. In addition, the volume of blood shifting between the trunk and the extremities over each breath – i.e. the amplitude of intra-breath Vbs swings – increased at all stages of the sequence with EFLe compared to CTRL.

Respiratory pressures and blood shift relationships during EFLe

Regression and correlation parameters between respiratory pressures and blood shift are shown in **Table 3**. Computation of Pearson's correlation coefficients and P-values between lung volume and respiratory pressures showed no strong association between pressures and Vbs parameters when only CTRL points were considered. However, after adding data obtained with EFLe - thus increasing the range of pressure and Vbs values - inspiratory Pes and expiratory Pga were found to be significantly associated with the changes in Vbs,OP during the corresponding phase, while inspiratory Pes and Pab and expiratory Pab were associated with corresponding Vbs,I-B values.

DISCUSSION

This study was designed to provide new insights into the respiratory and blood shifting effects of EFLe in healthy persons performing submaximal exercise. We built upon previous work that described the changes in breathing mechanics with EFLe and aimed to extend these results by providing, for the first time, a precise assessment of blood redistribution between body compartments. Specifically, we aimed to determine whether the decrease in venous return previously hypothesized with EFLe at maximal intensity would be observed during submaximal exercise. Our results indicate that with EFLe, each breath displaced a greater volume of blood between the thorax and the extremities, with a progressive net redistribution of blood into the thorax throughout exercise. Hereafter we propose potential explanations of these changes in light of our simultaneous assessment of breathing mechanics.

Breathing mechanics

A common feature of COPD is the development of high expiratory pressures with exercise (Potter *et al.*, 1971; Dodd *et al.*, 1984), which was previously reproduced with EFLe in healthy participants (Kayser *et al.*, 1997; Aliverti *et al.*, 2002; Iandelli *et al.*, 2002; Stark-Leyva *et al.*, 2004). Further examinations attributed these high expiratory pressures to the difficulty in increasing expiratory flow and the consequent slowing of expiratory muscles shortening (Aliverti *et al.*, 2002). Conversely EFLe increases inspiratory flow and thus increases inspiratory muscles shortening velocity. Our findings generally concur with these previous reports (**Figure 3 and Figure 5)**. From a mechanical standpoint, the decrease in peak inspiratory Pes observed with EFLe implies that inspiratory flow and inspiratory muscles shortening velocity were increased despite the concurrent increase in Tinsp (**Figure 3**). This suggests that the increase in inspiratory muscles lengthening

amplitude with EFLe was superior in magnitude to the increase in Tinsp. To support this contention, we analyzed the increase in the compartmental subdivision of Vcw corresponding to pulmonary rib cage (Vrcp) and calculated the ratio between the increase in Vrcp and Tinsp. We found an average increase in ΔVrcp/Tinsp of +61±22% with EFLe, suggesting that in this condition the velocity of shortening of the inspiratory muscles was indeed increased compared to the control condition.

Another frequent manifestation of COPD is the development of dynamic hyperinflation during exercise (O'Donnell & Webb, 1993). In fact, dynamic hyperinflation is often cited as a potential limiting factor of exercise tolerance in COPD patients (O'Donnell *et al.*, 1997; Bauerle *et al.*, 1998; O'Donnell, 2006; Aliverti *et al.*, 2008). However, the development of dynamic hyperinflation during exercise is not systematically observed in COPD, and different patterns of lung volume dynamics can be identified (Bauerle *et al.*, 1998; Aliverti *et al.*, 2004*b*). Inconsistencies in the development of dynamic hyperinflation were also previously reported in healthy persons performing incremental exercise with EFLe (Aliverti *et al.*, 2002; Iandelli *et al.*, 2002). Our findings show that on average, EELV increased with EFLe compared to the control condition (**Figure 4**). However, individual traces appeared to follow a range of different patterns. To apprehend this variability, each EFLe run was analyzed separately based on the dynamics of EELV. We calculated the mean and standard deviation of all breath-by-breath EELV values at rest during the CTRL runs for each participant and defined an individual threshold zone equal to mean±4SD. Each EFLe run was then assigned to one of three categories according to the observed EELV value during Ex3 (i.e. "below", "within" or "above" the threshold zone). This analysis showed that dynamic hyperinflation developed in 50% of total runs, while EELV remained stable in 43%, and decreased in only 7% (**Figure 7A**). In addition, because each participant repeated the same exercise sequence three times, our dataset revealed that not only dynamic hyperinflation did not occur in all participants, but that the heterogeneity of patterns followed by EELV could also be observed at the intra-individual level. Collectively, these findings confirm the variability of EELV dynamics previously observed in a healthy population experiencing EFLe (Aliverti *et al.*, 2002; Iandelli *et al.*, 2002) and in patients with COPD (Aliverti *et al.*, 2004*b*). Specifically, they indicate that different strategies of respiratory muscles recruitment can be adopted to cope with the load imposed by EFLe and demonstrate that the acute nature of EFLe comes with a certain degree of inter- and intra-individual variability. This variability can be further observed by examining the differences in both the flow-volume loops during exercise and the behavior of Tinsp between the three different breathing patterns (**Figure 8**). The impact of these differences in breathing mechanics on blood displacements is illustrated on **Figure 7B** and discussed hereafter.

Blood displacements

The hemodynamic analysis carried out with double body plethysmography in the present study showed that EFLe resulted in greater Vbs swings, indicating an increase in intra-breath blood displacements between the trunk and the extremities (**Figure 6**)**.** Moreover, during exercise, Vbs gradually decreased towards negative values, reflecting a net redistribution of blood into the trunk over time. Our measurements of Pes and Pga – used as estimates of intra-thoracic and intra-abdominal pressure, respectively– can help provide a mechanistic explanation for these hemodynamic changes. Indeed, it is well established that increasing intra-abdominal pressure can shift blood out of the abdominal compartment by compressing the splanchnic and hepatic vascular beds (Alexander, 1951; Takata *et al.*, 1990), while a drop in intra-thoracic pressure stimulates venous return by widening the pressure gradient between the peripheral and thoracic circulation (Guyton *et al.*, 1957). These interactions were further confirmed by exacerbating the amplitude of intra-abdominal and intra-thoracic pressure variations experimentally with voluntary expulsive maneuvers (Aliverti *et al.*, 2009, 2010) and inspiratory loading (Cheyne *et al.*, 2016, 2018), respectively. In addition, it was suggested that a greater decrease in intra-thoracic pressure could hinder left ventricular stroke volume through direct ventricular interaction – that is, the increase in right ventricular filling would reduce left ventricular compliance – and increase afterload (Cheyne *et al.*, 2020), although these effects remain unclear during exercise (Cheyne *et al.*, 2018). In previous work, we found that during exercise, 'abdominal' and 'rib cage' breathing maneuvers, designed to selectively increase intra-abdominal and intra-thoracic pressure swings by emphasizing the action of the diaphragm and the rib cage muscles, respectively, resulted in an increase in Vbs swings compared to spontaneous breathing (Uva *et al.*, 2016; Stucky *et al.*, 2021).

In the presents study, the observed increase in intra-breath Vbs swings with EFLe could therefore be explained by the corresponding combination of high expiratory intra-abdominal pressure expelling blood out of the abdominal compartment and low inspiratory intra-thoracic pressure drawing blood into the thorax from the extremities (**Figure 5**). Furthermore, the concurrent progressive decrease in Vbs seen during exercise with EFLe indicates that for each breath the inspiratory inflow of blood into the trunk was repeatedly greater than the expiratory outflow towards the extremities, thus resulting in a gradual redistribution into the trunk over time (**Figure 6**). Yet, it was previously hypothesized that the development of high expiratory pressures with EFLe would act like a Valsalva maneuver and thus decrease venous return and cardiac output (Potter *et al.*, 1971; Iandelli *et al.*, 2002; Aliverti *et al.*, 2005). Indeed, increasing intra-abdominal pressure beyond a certain level can lead to a momentary halting of femoral venous return due to the consequent decrease in the pressure gradient between the thorax and the periphery (Miller *et al.*,

2005*a*, 2005*b*). While it is well possible that the EFLe-driven increase in intra-abdominal and intra-thoracic pressure reduced venous return during expiration in our study, the dynamics of Vbs indicate that any potential impediment was counteracted by a greater inflow into the trunk during inspiration.

Our analysis of the relationships between respiratory pressure and Vbs during exercise support our interpretation (**Table 3, Figure 9**). Indeed, we found that the intra-breath Vbs variations were positively associated with Pes during inspiration and with Pab during expiration, confirming that the alternation between lower inspiratory intra-thoracic and higher expiratory intra-abdominal pressure values play a role in the increase in intra-breath Vbs swings with EFLe. Further analyses revealed that the relationship between intra-breath Vbs and Pes during inspiration could be better described using an exponential function rather than a linear regression (R^2 = 0.408 vs 0.292, respectively) (**Figure 9B**). From a physiological standpoint, the use of an exponential model implies that average inspiratory Pes must drop below a certain level to effectively produce a detectable displacement of blood into the trunk. Thus, assuming a 'detection' threshold value of 50 ml for intra-breath Vbs (Aliverti *et al.*, 2009, 2010), our data show that this critical average Pes value throughout inspiration would be located around -14 cmH_2O (**Figure 9B**). In addition to the intra-breath effect of respiratory pressures, the drop in operational Vbs compared to baseline over time was positively associated with inspiratory Pes, but negatively associated with expiratory Pga. These results suggest that the lower intra-thoracic pressure observed with EFLe was the driving force for blood redistribution into the trunk. We thus speculate that the progressive redistribution of blood into the thorax observed with EFLe was mainly driven by the greater recruitment of inspiratory lung volume and the consequently greater drops in intra-thoracic pressure, drawing blood from the peripheral circulation. This phenomenon is also illustrated by the qualitative differences in Vbs patterns in function of our classification based on EELV levels during exercise, where the decrease in operational Vbs was more pronounced during the 'hyperinflator' runs, where Pes decreased more drastically due to greater EILV levels (**Figure 7**). As hypothesized in previous experiments, this inflow of blood into the trunk from the extremities may be partly accommodated by the recruitment of the low resistance and high capacitance pulmonary vascular system (Flamm *et al.*, 1990).

Previous experiments associated the development of high expiratory pressure in EFLe with a reduction in venous return (Potter *et al.*, 1971; Iandelli *et al.*, 2002; Stark-Leyva *et al.*, 2004; Aliverti *et al.*, 2005), and speculated that such alteration of the respiratory pump mechanism would in turn contribute to limit exercise tolerance (Aliverti *et al.*, 2007, 2008). Our assessment of Vbs, showing a net displacement of blood into the trunk during EFLe exercise contrasts with this hypothesis. Such divergence suggests that the hemodynamic effect of EFLe may differ according to the intensity of

exercise. At maximal intensity, it is indeed likely that a more pronounced increase in expiratory pressure would develop and become a more prominent contributor to blood displacement. Indeed, peak expiratory values as high as ~55 and ~45 cmH_2O have been reported for Pga and Pes at maximal intensity, respectively, while our estimations during the final minute of submaximal exercise amounted only to 29.2±6.1 and 13.2±10.5 cmH_2O (**Figure 5**). Moreover, the rate of dynamic hyperinflation reported herein was substantially higher than previous observations (Aliverti *et al.*, 2002; Iandelli *et al.*, 2002). Indeed, a decrease in EELV during exercise was only evident in a minority of cases (7% of total runs), which suggests that most runs were performed with the increase in EILV as the main strategy to cope with EFLe, as opposed to a dramatic recruitment of expiratory muscles to increase Vt and limit hypoventilation. Finally, the submaximal intensity used in our protocol (corresponding to ~40% $\dot{V}O_2max$) was sufficiently low to enable Tinsp to increase with EFLe compared to CTRL, whereas a systematic decrease in Tinsp was previously reported at maximal intensity (Kayser *et al.*, 1997; Iandelli *et al.*, 2002; Aliverti *et al.*, 2005). In our study, although duty cycle substantially decreased because of the more pronounced increase in Texp, the increase in Tinsp may have been just sufficient to allow the inspiratory inflow of blood into the trunk to override the expiratory outflow.

Relevance to COPD

The unique setup used in the present study enabled, for the first time, to collect measurements of blood displacements between body compartments during submaximal exercise with EFLe, in conjunction with a comprehensive assessment of breathing mechanics. Unlike previous investigations that studied the effects of EFLe during incremental tests to exhaustion, our protocol involved submaximal exercise, which can be considered more akin to what patients with COPD would experience in their daily lives. Our findings confirm that healthy participants exercising with EFLe exhibit changes in breathing mechanics comparable to what has been observed in COPD patients, with dynamic hyperinflation developing in some cases but not all. This suggests that EFLe is a useful experimental tool to study breathing mechanics within the constraints specifically associated with expiratory flow limitation during exercise and can be used to make reasonable inferences regarding pathological situations without the risks associated with exercise in patients. With regards to blood redistribution specifically, it is uncertain whether the results obtained with EFLe can be generalized to patients with COPD. Indeed, the pathophysiological manifestations of COPD are not constrained to expiratory flow limitation and most commonly include an array of comorbidities potentially affecting hemodynamics and including some inspiratory limitation as well (Cavaillès *et al.*, 2013). The translocation of blood from the extremities towards the trunk reported

herein with EFLe implies that a certain amount of this supplemental blood would be accommodated in the high capacitance and low resistance pulmonary vasculature. In the present investigation, we studied healthy active young men, and although not specifically endurance trained, some of them with above-average aerobic capacity (**Table 1**), whose cardiovascular properties would likely substantially differ from COPD patients. Indeed, in COPD, the normal physical properties of the pulmonary vascular bed are often altered by factors including pulmonary vascular bed destruction resulting from emphysema, hypoxic pulmonary vasoconstriction, polycythemia and pulmonary vascular endothelial dysfunction (Shujaat *et al.*, 2007), which altogether increase pulmonary vascular resistance and lead to pulmonary hypertension and ultimately right ventricular dysfunction (i.e. cor pulmonale). Consequently, similar investigations using double body plethysmography in patients with COPD are warranted to gain further insights into the function of the respiratory pump during submaximal exercise in this population.

Limitations

The technical achievements presented in this study come with their limitations. First, the hemodynamic data obtained with double body plethysmography are presented as blood shifting within a two-compartment model (trunk vs extremities). The measurement of trunk volume does not discern the abdominal and thoracic subdivisions, which precludes the estimation of blood redistribution between them. Furthermore, Vbs is measured as an absolute volume which encompasses both arterial outflow and venous inflow without the possibility of distinguishing one from the other. Second, given the small sample size and the presumption of modest effect size, we aimed to minimize any sources of potential variability and thus focused this initial analysis on one biologic sex. Inclusion of women would have necessitated increasing the number of included participants in order to allow comparison since there are differences between men and women with regard to the physiological responses to submaximal exercise (increased cardiac work, greater peripheral oxygen extraction, decreased energy expenditure, greater efficiency) (Wheatley *et al.*, 2014) and differing respiratory mechanics (Dominelli & Molgat-Seon, 2022). Extending this experimental work into different participant groups will represent an important topic of future research. Third, we did not monitor respiratory CO_2 levels and therefore cannot evaluate the impact of EFLe on hypercapnia during submaximal exercise. Fourth, because of the constraints of our setup, we did not measure cardiovascular variables. Doing so would have allowed a more comprehensive capture of our experimental intervention. Fifth, our custom-made cycle ergometer restrained the exercise protocol to a fixed absolute workload (100 W) for all participants. Individualizing the intensity (e.g. a given percentage of individual peak incremental work rate) would have potentially

reduced experimental noise. Finally, in our calculations of VL we used age, sex and size estimates of FRC instead of measured values.

CONCLUSION

Our findings indicate that during submaximal exercise, EFLe produced greater intra-breath blood displacements between the trunk and the extremities with a progressive redistribution of blood into the thorax. These effects resulted from the cyclical increase in intra-abdominal and intra-thoracic pressure during expiration and decrease in intra-thoracic pressure during inspiration, with a more prominent inspiratory inflow accumulating blood into the trunk over time. We speculate that the contrast between our results and those previously obtained at peak exercise intensity can be attributed to the less pronounced recruitment of expiratory muscles at submaximal level. Whether these results can be replicated in COPD patients is unclear and remains to be determined.

ADDITIONAL INFORMATION

Data Availability: Data from this study will be made available upon reasonable request to corresponding author.

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Competing interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Authors contributions

Conception and design of research: F.S., B.U., A.A. and B.K. Acquisition, analysis, and interpretation of data: F.S., B.U., A.A. and B.K. Drafting manuscript and critical revision: F.S., B.U., A.A. and B.K. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Table 1 : Participant characteristics and exercise intensity

Age	(year)		25±3
Height	(cm)		177.3±5.4
Weight	(kg)		67.4±5.8
$\dot{V}O_2max$	($L \cdot min^{-1}$)		3.671±0.56
$\dot{V}O_2$ Ex3	($L \cdot min^{-1}$)	*CTRL*	1.437±0.18
		EFLe	1.511±0.15
$\dot{V}O_2$ Ex3	(%$\dot{V}O_2max$)	*CTRL*	39±6
		EFLe	42±6

Means±SD; $\dot{V}O_2$peak = absolute peak oxygen uptake; $\dot{V}O_2$ Ex3 = oxygen uptake during the final minute of exercise; %$\dot{V}O_2$peak = percentage of absolute $\dot{V}O_2$peak during the final minute of exercise; CTRL = control condition; EFLe = externally imposed expiratory flow limitation. N=10.

Table 2: Respiratory and hemodynamic parameters averaged over 60-s slots at rest and during exercise and recovery

	REST			EX1			EX2			EX3			REC1			REC2		
	CTRL	EFLe	P	CTRL	EFLe	P	CTRL	EFLe	P	CTRL	EFLe	P	CTRL	EFLe	P	CTRL	EFLe	P
Vt (L)	0.8±0.2	1.9±0.7	<0.001	1.2±0.3	2.7±0.9	<0.001	1.5±0.3	3.2±0.8	<0.001	1.6±0.4	3.2±0.9	<0.001	1.5±0.3	2.7±0.9	<0.001	1.0±0.2	2.2±0.9	<0.001
RR (br.min-1)	17±3.2	8.9±2.5	<0.001	23.8±4.3	8.8±2.6	<0.001	27.6±5.6	9.6±3.1	<0.001	29.1±5.8	11.7±4.9	<0.001	21.2±4.1	11.9±4.4	<0.001	19.3±3.9	10.9±3.7	<0.001
VE (L.min-1)	13.7±3	16.2±4.5	0.018	27.8±3.6	21.7±3.4	<0.001	39.1±5.1	28.5±4.9	<0.001	44.2±6.8	33.5±7.1	<0.001	31.7±6.5	29.8±7.6	0.333	19.5±4.7	21.6±6.5	0.167
Tinsp (s)	1.5±0.3	2.4±0.7	<0.001	1.3±0.4	2.3±0.8	<0.001	1.1±0.4	2.0±0.6	<0.001	1.0±0.3	1.7±0.5	<0.001	1.3±0.2	1.5±0.4	0.008	1.3±0.3	1.7±0.5	0.003
Texp (s)	2.3±0.6	4.9±1.5	<0.001	1.6±0.3	5.2±1.5	<0.001	1.2±0.3	5.0±1.7	<0.001	1.2±0.2	4.4±2	<0.001	1.7±0.4	4.3±1.8	<0.001	2.0±0.4	4.6±1.8	<0.001
Duty cycle	0.40±0.06	0.33±0.06	<0.001	0.45±0.03	0.32±0.06	<0.001	0.46±0.03	0.3±0.06	<0.001	0.46±0.02	0.29±0.07	<0.001	0.43±0.03	0.28±0.05	<0.001	0.41±0.05	0.28±0.06	<0.001
EILV (L)	0.7±0.2	1.8±0.7	<0.001	0.8±0.4	2.5±0.9	<0.001	1.0±0.4	2.8±0.9	<0.001	1.0±0.5	2.9±1	<0.001	1.1±0.3	2.7±0.8	<0.001	0.7±0.2	2.1±0.8	<0.001
EELV (L)	0.0±0.1	0.3±0.3	<0.001	-0.2±0.2	0.3±0.5	<0.001	-0.2±0.3	0.4±0.6	<0.001	-0.2±0.3	0.6±0.7	<0.001	-0.1±0.2	0.8±0.6	<0.001	-0.1±0.2	0.5±0.5	<0.001
Pes peak insp (cmH_2O)	-12±4.1	-17.3±3.9	<0.001	-14±3.8	-23.4±5.8	<0.001	-16.4±4.6	-28.4±8	<0.001	-17.3±4.9	-29.7±9.7	<0.001	-16.4±5	-26.9±7.7	<0.001	-13.8±4.4	-19.5±4.9	<0.001
Pes peak exp (cmH_2O)	-4.6±4.1	2.0±7.1	<0.001	-1.7±5.8	6.1±6.7	<0.001	-0.1±8.5	10.3±7.8	<0.001	1.0±10.3	13.3±8.5	<0.001	-1.8±7.3	8.5±7.6	<0.001	-4.1±5.4	2.8±6.4	<0.001
Pga peak insp (cmH_2O)	4.5±2.4	3.4±2.4	0.078	5.7±2.9	2.9±3.8	0.003	5.7±3.2	1.9±4	<0.001	5.7±2.8	2±4.4	<0.001	3.3±2.9	1.2±4	0.025	3.3±2.6	2.2±3.2	0.163
Pga peak exp (cmH_2O)	9.3±3.8	15.3±4.4	<0.001	12.3±4.1	22.2±6	<0.001	13.1±4.5	25.7±6	<0.001	13.1±4.3	29.2±6.1	<0.001	10.2±4.4	21.9±7.9	<0.001	9.0±4.2	16±5.5	<0.001
Vbs (L)	-0.02±0.05	-0.07±0.13	0.048	-0.05±0.28	-0.33±0.34	0.001	-0.13±0.31	-0.56±0.45	<0.001	-0.15±0.31	-0.69±0.53	<0.001	-0.15±0.24	-0.68±0.43	<0.001	-0.05±0.22	-0.36±0.33	<0.001
Vbs swings	0.12±0.03	0.25±0.17	<0.001	0.22±0.05	0.45±0.25	<0.001	0.22±0.06	0.51±0.25	<0.001	0.22±0.06	0.52±0.22	<0.001	0.17±0.05	0.42±0.23	<0.001	0.14±0.0	0.3±0.18	<0.001

(L)					1	3	1

EX1,2,3 = average values over the first, second and third minute of exercise; REC= recovery; CTRL= normal breathing; EFLe: external expiratory flow limitation; Vt = tidal volume; RR = respiratory rate; V'E=ventilation; Tinsp = inspiratory time; Texp = expiratory time; EILV, EELV= end-inspiratory and end-expiratory lung volume (relative to FRC), respectively; Pes peak insp, exp= peak inspiratory and expiratory esophageal pressure, respectively, Pga = gastric pressure; Vbs = volume of blood shift; Vbs swings = intra-breath Vbs amplitude.

Table 3 : Linear regression and correlation parameters during the last minute of exercise.

		ALL			EFLe			CTRL		
		Pearson	**R^2**	**P-Value**	**Pearson**	**R^2**	**P-Value**	**Pearson**	**R^2**	**P-Value**
Pes *vs* Vbs,OP	INSP	**0.540**	**0.292**	**<0.001**	**0.620**	**0.385**	**<0.001**	0.098	0.010	0.608
Pes *vs* Vbs,OP	EXP	-0.092	0.008	0.487	**0.423**	**0.179**	**0.020**	0.031	0.001	0.869
Pga *vs* Vbs,OP	INSP	-0.061	0.004	0.641	-0.128	0.016	0.499	-0.236	0.056	0.210
Pga *vs* Vbs,OP	EXP	**-0.526**	**0.277**	**<0.001**	-0.312	0.098	0.093	-0.156	0.024	0.410
Pes *vs* Vbs,I-B	INSP	**0.533**	**0.284**	**<0.001**	**0.544**	**0.296**	**0.002**	0.179	0.032	0.344
Pes *vs* Vbs,I-B	EXP	0.137	0.019	0.296	**0.423**	**0.179**	**0.020**	0.098	0.010	0.605
Pab *vs* Vbs,I-B	INSP	**0.407**	**0.166**	**0.001**	0.052	0.003	0.784	-0.337	0.113	0.069
Pab *vs* Vbs,I-B	EXP	**0.291**	**0.085**	**0.024**	0.230	0.053	0.221	-0.096	0.009	0.614

Pes = esophageal pressure; Pga = gastric pressure; Pab = abdominal pressure; Vbs,OP = operational Vbs relative to quiet breathing; Vbs,I-B = intra-breath variations in Vbs; INSP, EXP = average values during inspiration and expiration, respectively. CTRL, EFLe, ALL = regression and correlation parameters computed for points in control condition, during external expiratory flow limitation, or all points considered (CTRL and EFLe), respectively.

Figure 1

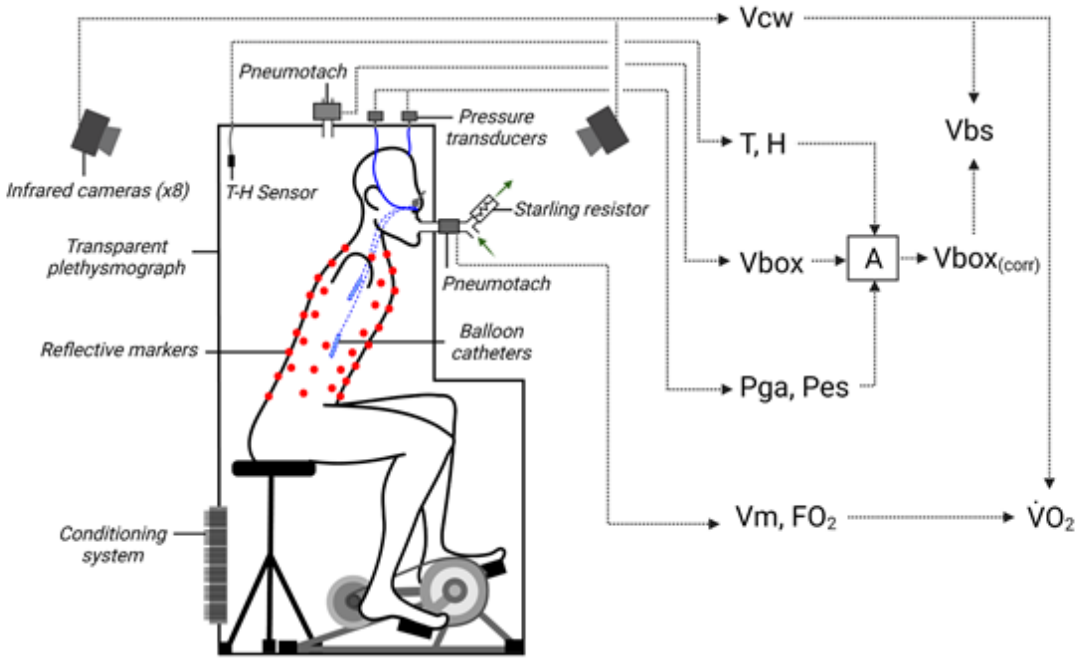

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Figure 1: Schematic representation of the experimental setup. Vcw=Chest wall volume; T= Temperature; H= Humidity; Vbs= volume of blood shifts; Vbox= volume derived from airflow in and out of the plethysmograph; A= algorithm used to correct Vbox drift; Pga, Pes= gastric and esophageal pressures, respectively; Vm= volume derived from airflow measured at the mouth; FO2=O2 fraction at the mouth; $\dot{V}O_2$= oxygen uptake.

Figure 2

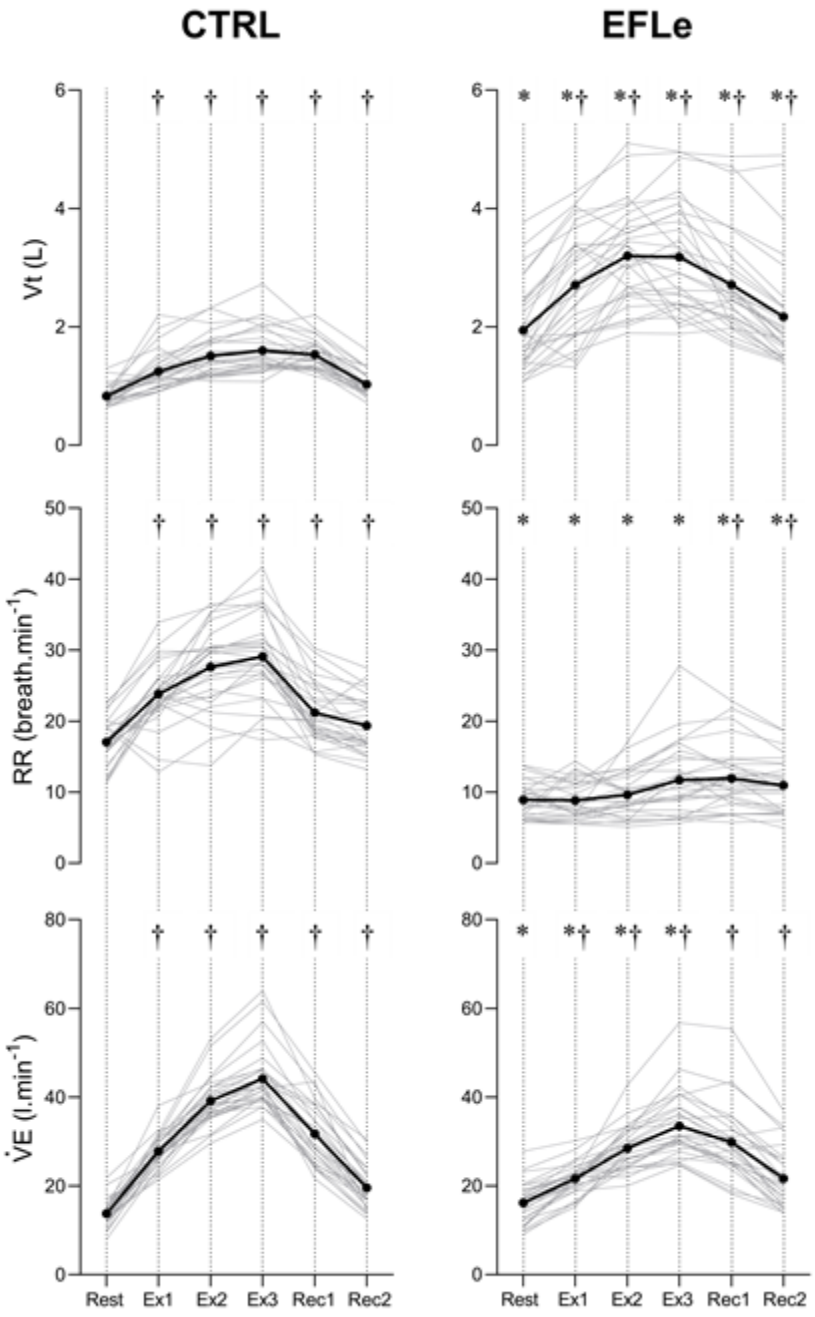


Figure 2: Tidal volume (Vt, top) Respiratory rate (RR, middle), and minute ventilation (V̇E, bottom) over time during a sequence of 1min rest, 3 minutes of constant-load exercise (Ex1,2,3) and 2 minutes of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without EFLe (CTRL). Values are calculated breath-by-breath and averaged over each period. Light, thinner lines represent a single sequence for one participant; Darker, thicker lines and dots represent the average value calculated for each period from all single sequences. † Different from Rest; *Different from CTRL (P<0.05). N=10.

Figure 3

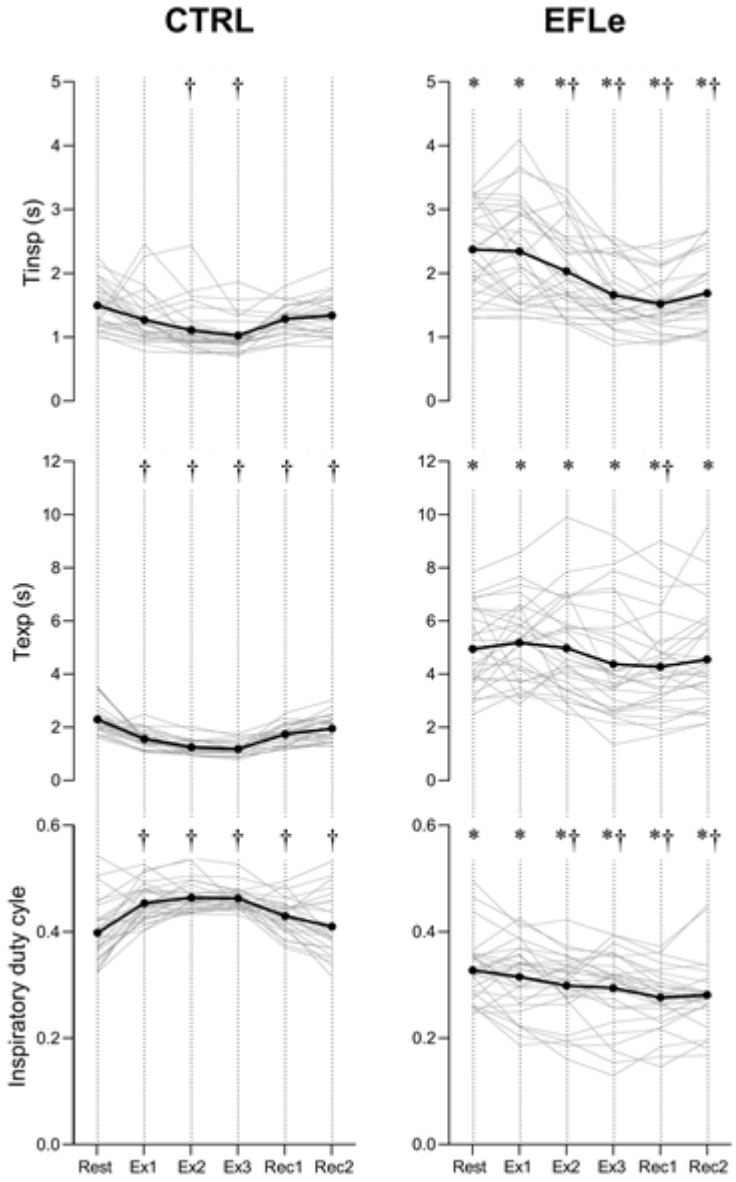


Figure 3: Inspiratory time (Tinsp, top), expiratory time (Texp, middle) and inspiratory duty cycle (Ti/Ttot, bottom) over time during a sequence of 1min rest, 3 minutes of constant-load exercise (Ex1,2,3) and 2 minutes of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without EFLe (CTRL). Values are calculated breath-by-breath and averaged over each period. Light, thinner lines represent a single sequence for one participant; Darker, thicker lines and dots represent the average value calculated for each period from all single sequences. † Different from Rest; *Different from CTRL (P<0.05). N=10.

Figure 4

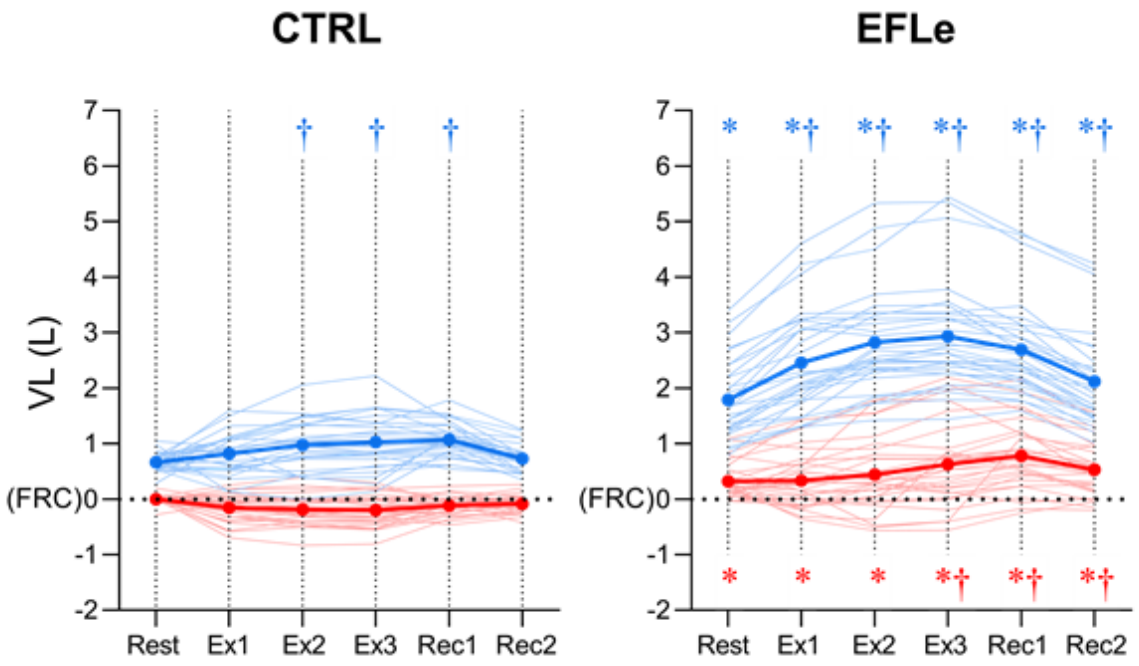


Figure 4: End-inspiratory (blue) and end-expiratory (red) lung volume over time during a sequence of 1 min rest, 3 minutes of constant-load exercise (Ex1,2,3) and 2 minutes of recovery (Rec1,2) with (EFLe) and without EFLe (CTRL). Values are calculated breath-by-breath and averaged over each period. Data are reported as variations from FRC (FRC=0) calculated as the average end-expiratory point over the resting period during CTRL. Light, thinner lines represent a single sequence for one participant; Darker, thicker lines and dots represent the average value calculated for each period from all single sequences. † Different from Rest; *Different from CTRL (P<0.05). N=10.

Figure 5

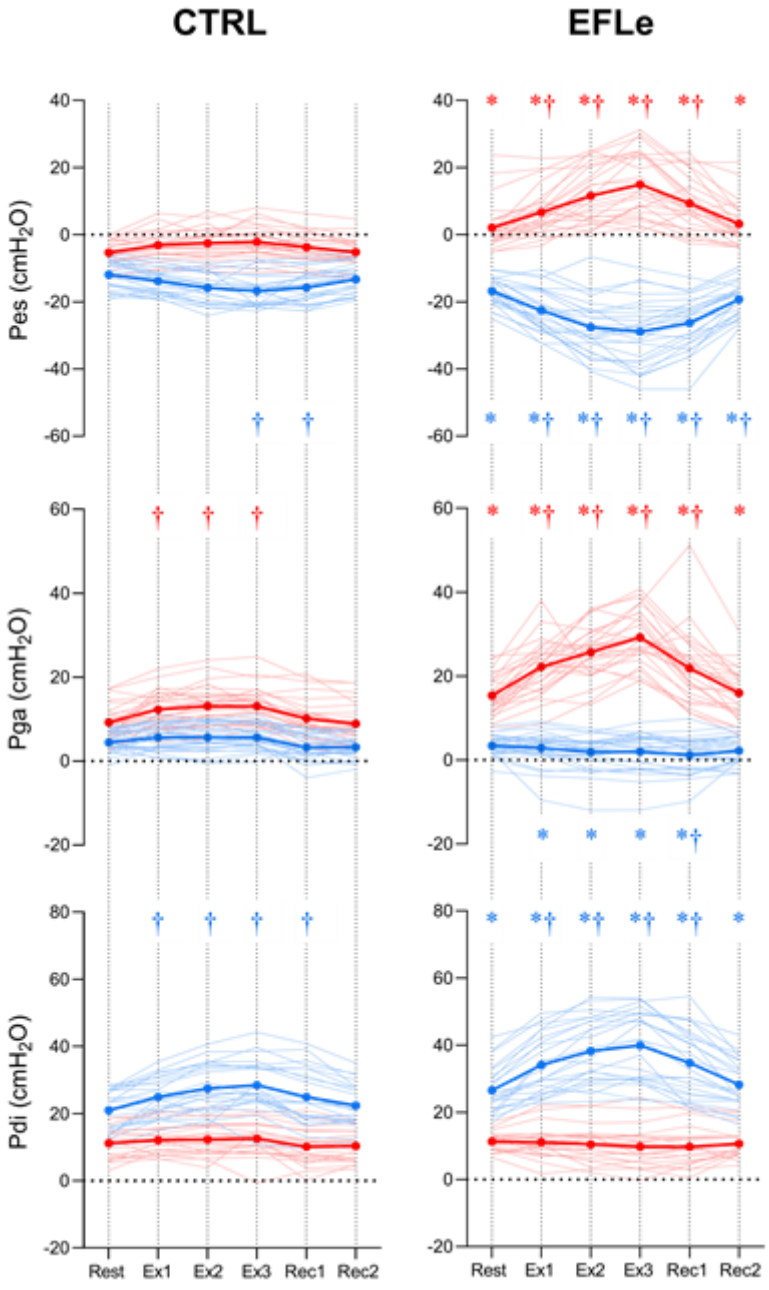


Figure 5: Peak inspiratory (blue) and expiratory (red) esophageal (Pes, top panel), gastric (Pga, middle panel) and transdiaphragmatic pressure (Pdi, bottom panel) over time during a sequence of 1min rest, 3 minutes of constant-load exercise (Ex1,2,3) and 2 minutes of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without EFLe (CTRL). Signals are averaged over each period. Light, thinner lines represent a single sequence for one participant; Darker, thicker lines and dots represent the average value calculated for each period from all single sequences. † Different from Rest; *Different from CTRL (P<0.05). N=9.

Figure 6

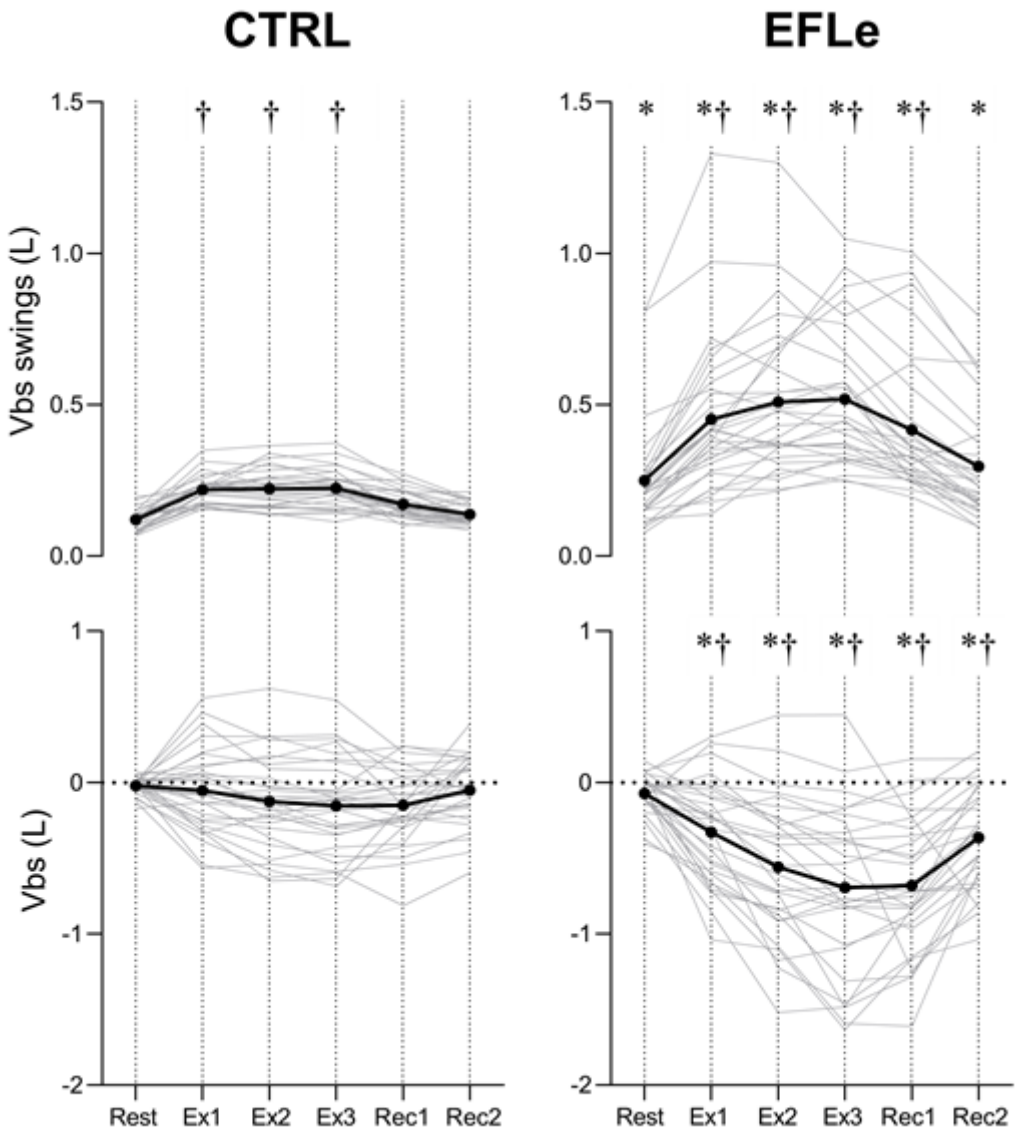


Figure 6: Volume of blood shift (Vbs, bottom panel) and intra-breath Vbs amplitude (Vbs swings, top panel) over time during a sequence of 1 min rest, 3 minutes of constant-load exercise (Ex1, 2, 3) and 2 minutes of recovery (Rec1, 2) with externally imposed expiratory flow limitation (EFLe) and without EFLe (CTRL). For Vbs, the signal is averaged over each period. For Vbs swings, values are calculated breath-by-breath and averaged over each period. Light, thinner lines represent a single sequence for one participant; Darker, thicker lines and dots represent the average value calculated for each period from all single sequences. † Different from Rest; *Different from CTRL (P<0.05). N=10.

Figure 7

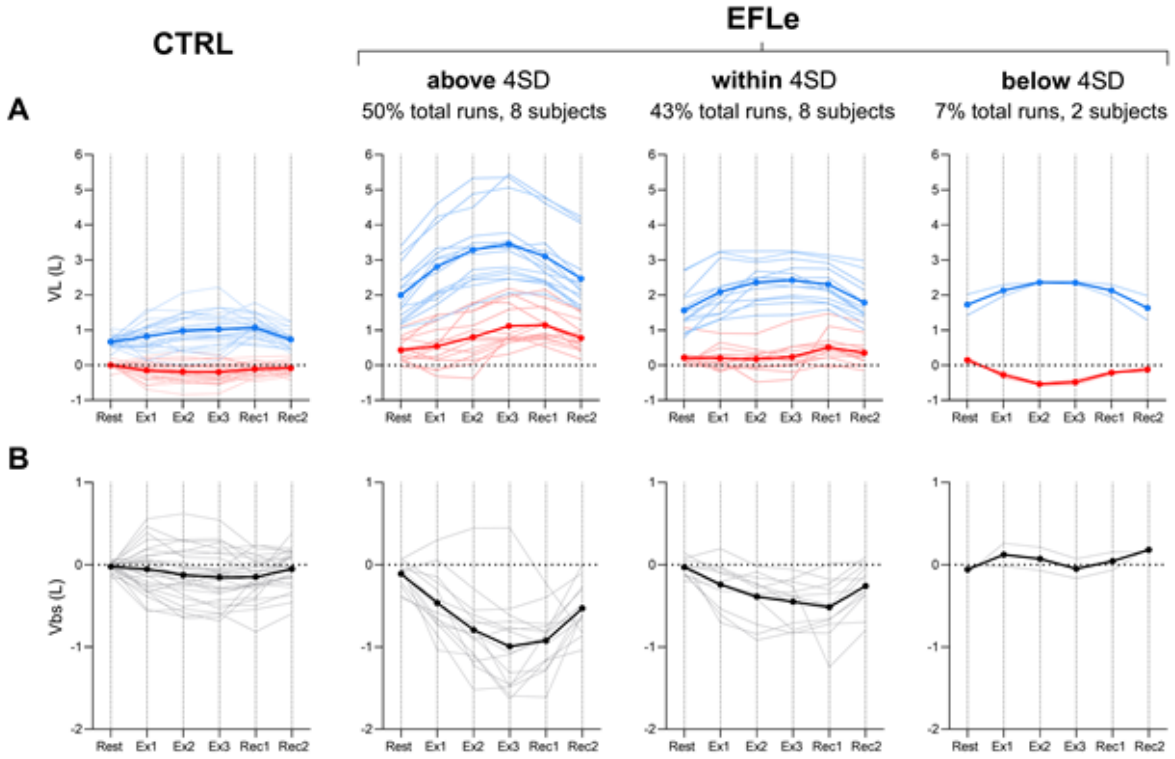


Figure 7 **: A:** Classification of end expiratory lung volume (EELV) dynamics during exercise with externally applied expiratory flow limitation (EFLe). A threshold zone is defined as the mean EELV value during resting control (CTRL 'Rest' = 'zero' line) plus or minus 4 standard deviations for each participant. EFLe runs are then assigned to three different categories ('above', 'within' or 'below') based on the EELV value observed during the final minute of exercise (Ex3) relative to the individual threshold zone. Red and blue lines and dots are mean EELV and end-inspiratory lung volume values, respectively. Individual traces are shown in lighter colors. **B:** Volume of blood shift (Vbs) during control (CTRL) and with externally applied expiratory flow limitation (EFLe). EFLe runs are categorized according to the pattern followed by EELV during exercise. Black lines and dots are mean Vbs, grey lines show individual values. N=10.

Figure 8

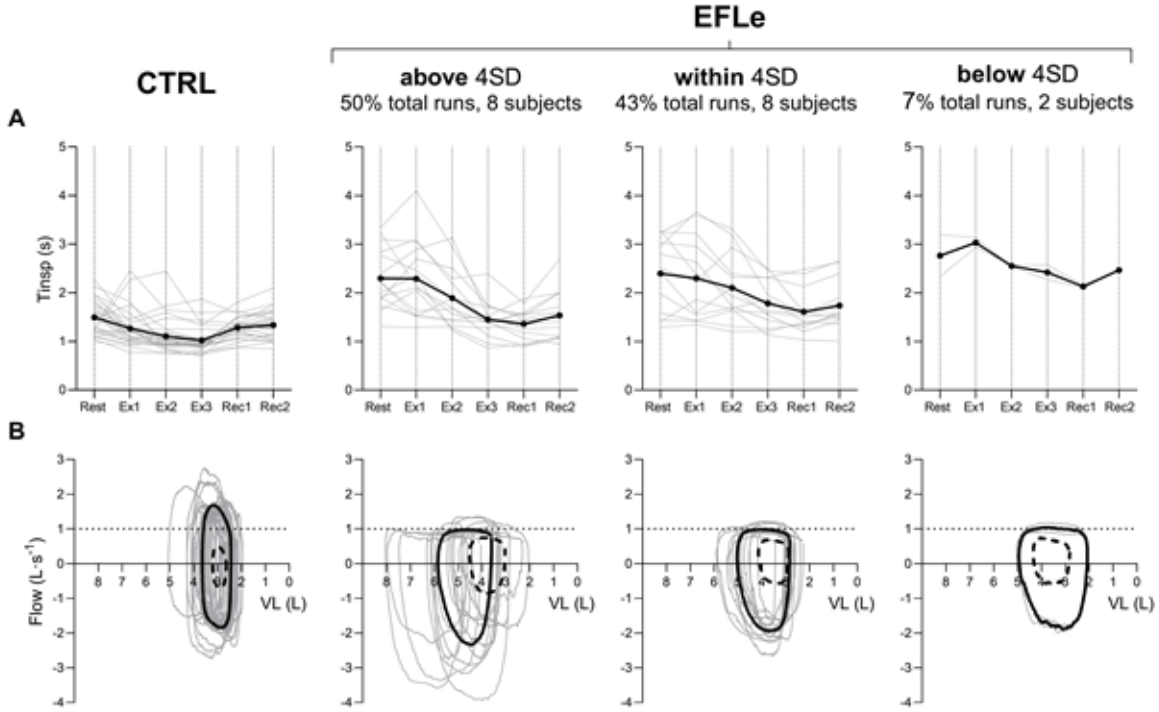


Figure 8 : A: inspiratory time (Tinsp) traces during control (CTRL) and with induced expiratory flow limitation (EFLe), categorized according to the pattern followed by EELV during exercise. B: corresponding flow-volume loops at rest (dashed lines) and during the last minute of exercise (Ex3, solid lines). N=10.

Figure 9

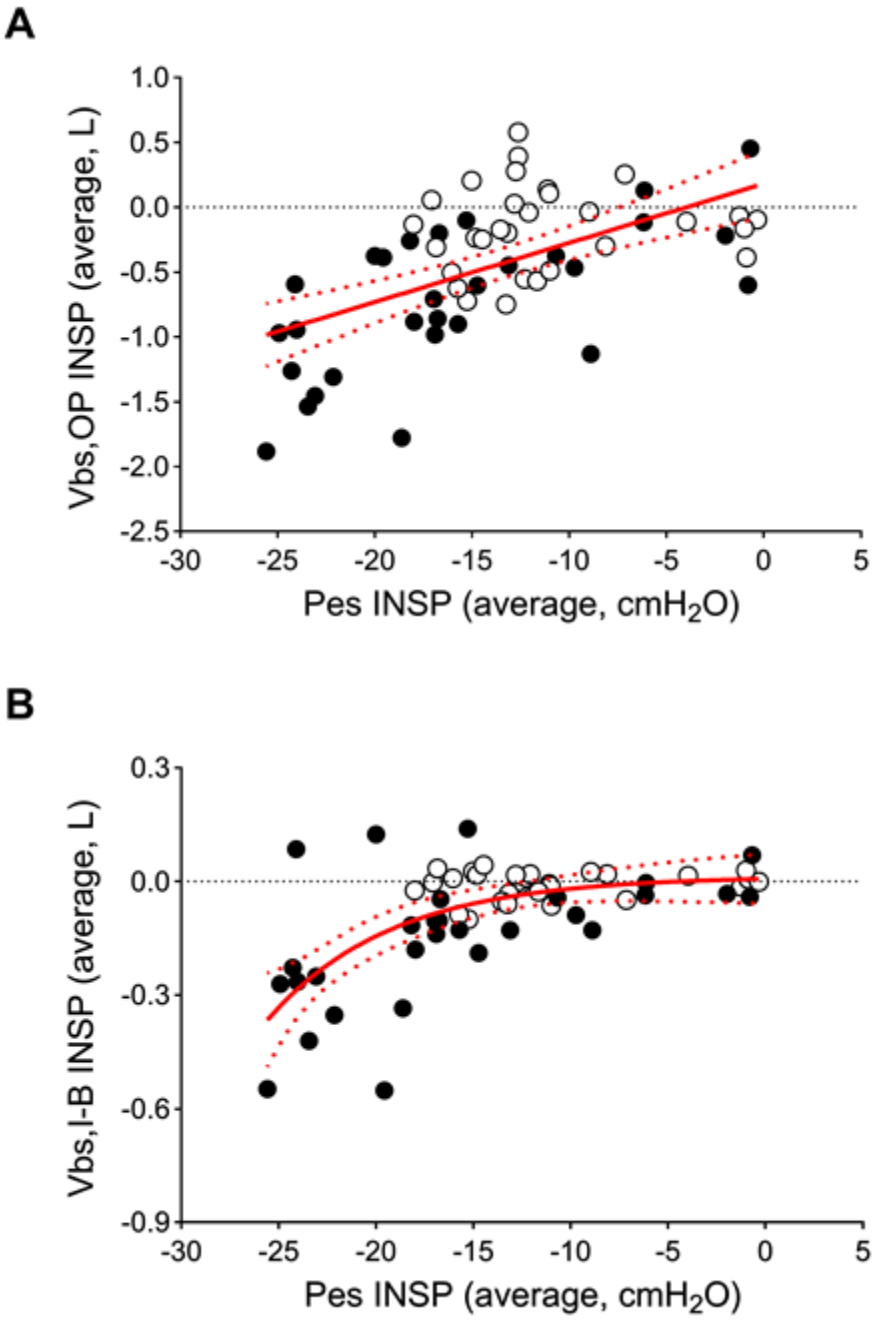
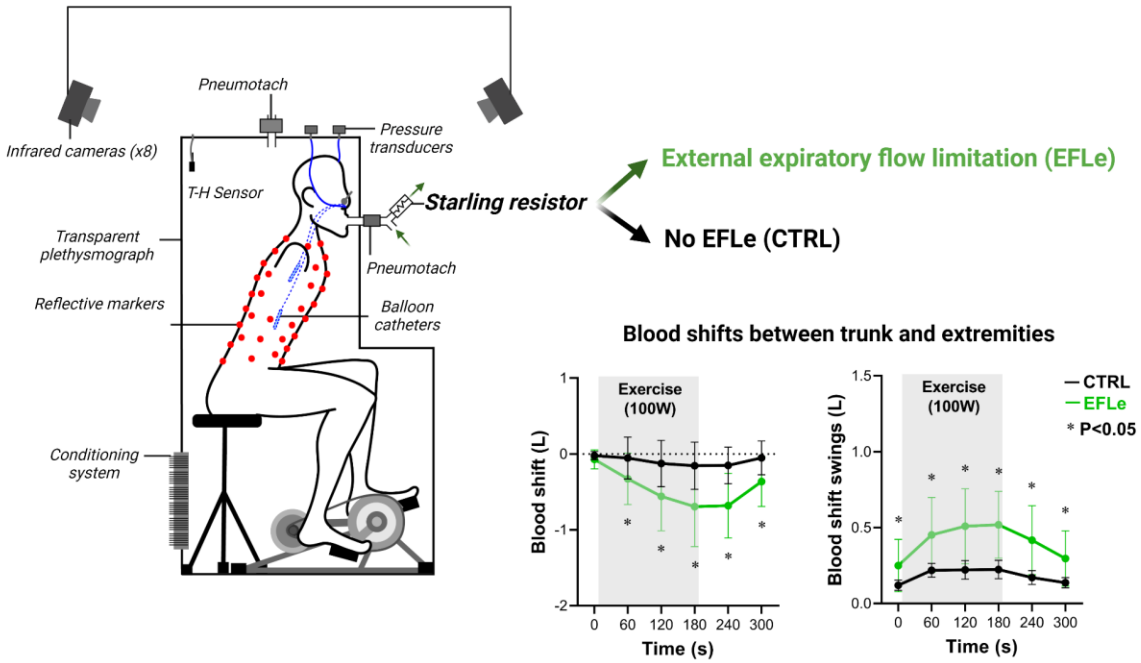


Figure 9 : Relationship between mean values of esophageal pressure and (A) operational volume of blood shift (Vbs,OP), (B) intra-breath blood shifts (Vbs,I-B) during inspiration within the last minute of exercise. Data points during spontaneous breathing (○) and externally imposed expiratory flow limitation (●) are represented. Solid red lines are linear and exponential regressions, respectively; dotted red lines are 95% confidence bands. N=9.

Frédéric Stucky obtained a B.Sc. and M.Sc. in Movement and Sport Sciences at the University of Geneva. He conducted this study as a Ph.D. student in the laboratory of Prof. Bengt Kayser at the University of Lausanne, where he examined the impact of respiratory mechanics on the cardiovascular response to exercise. He then refined his research experience as a Visiting researcher in the laboratory of Prof. Andrea Aliverti at the Polytechnic University of Milan and will continue investigating respiratory and cardiovascular interactions during exercise.



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Abstract figure legend Quantification of blood shifting between the trunk and the extremities by double plethysmography (total body and optoelectronic plethysmography). The volume of blood shifted (Vbs) from the extremities to the trunk and intra-breath Vbs amplitude (swings) significantly increase during submaximal exercise with externally applied expiratory flow limitation (EFLe).