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

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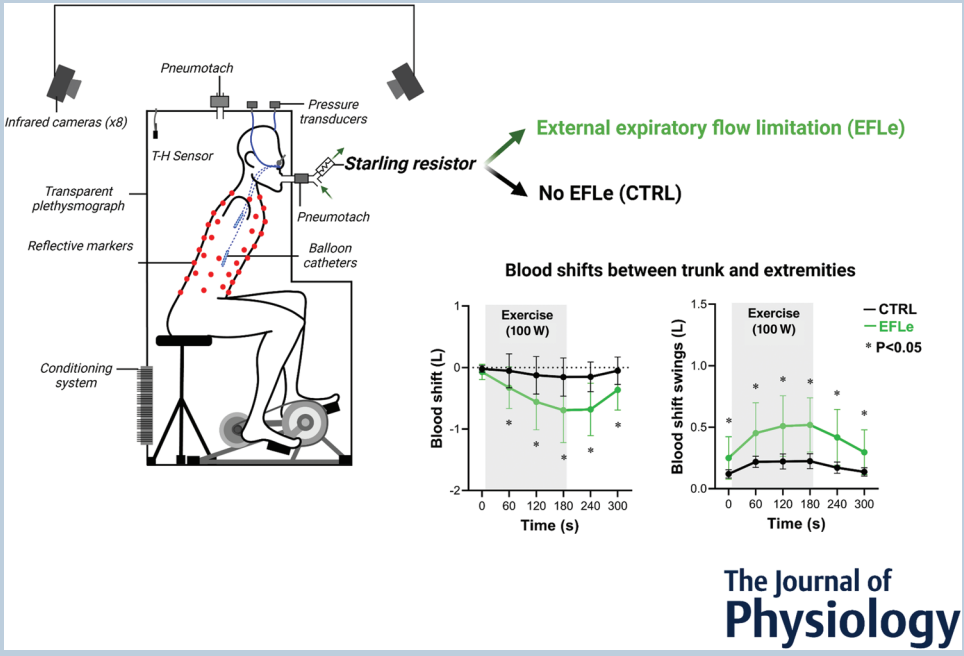
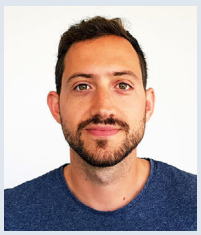


Abstract External expiratory flow limitation (EFLe) can be applied in healthy subjects to mimic the effects of chronic obstructive pulmonary disease during exercise. At maximal exercise intensity, EFLe leads to exercise intolerance owing to respiratory pump dysfunction limiting venous return. We quantified 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 years of age, 177.3 ± 5.4 cm in height and weighing 67.4 ± 5.8 kg) exercised at 100 W (~40% of maximal oxygen uptake) while breathing spontaneously (CTRL) or with EFLe. We

Frédéric Stucky obtained a BSc and MSc in Movement and Sport Sciences at the University of Geneva. He conducted the present study as a PhD student in the laboratory of Professor 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 Professor Andrea Aliverti at the Polytechnic University of Milan and will continue to investigate respiratory and cardiovascular interactions during exercise.



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measured respiratory dynamics with optoelectronic plethysmography, oesophageal (P_{es}) and gastric (P_{ga}) pressures with balloon catheters, and blood shifting between body compartments with double body plethysmography. During exercise, EFLe resulted in the following changes: (i) 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 P_{es} during inspiration ($r = 0.53$, $P < 0.001$) and higher P_{ga} during expiration ($r = 0.29$, $P < 0.024$); and (ii) a progressive pooling of blood in the trunk over time (∼700 ml after 3 min of exercise; $P < 0.05$), explained by a predominant effect of lower inspiratory P_{es} ($r = 0.54$, $P < 0.001$) over that of increased P_{ga}. It follows that during submaximal exercise, EFLe amplifies the respiratory pump mechanism, with a prevailing contribution from lower inspiratory P_{es} over increased expiratory P_{ga}, drawing blood into the trunk. Whether these results can be replicated in chronic obstructive pulmonary disease patients remains to be determined.

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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 intrabreath Vbs amplitude (swings) increase significantly during submaximal exercise with externally applied expiratory flow limitation (EFLe).

Key points

- External expiratory flow limitation (EFLe) can be applied in healthy subjects to mimic the effects of chronic obstructive pulmonary disease 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 to 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 intrathoracic pressure progressively drawing blood into the trunk.
- These results help us to understand the haemodynamic effects of respiratory pressures during submaximal exercise with expiratory flow restriction.

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, in a series of investigations the expiratory flow was limited 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 (Aliverti et al., 2002; Iandelli et al., 2002; Kayser et al., 1997). Given its transitory nature when imposed in healthy persons, EFLe allows exercise 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 manoeuvres increasing intra-abdominal pressure during expiration can result in a temporary halting of venous return from the extremities (Miller et al., 2005a, b). Accordingly, a reduction 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 displacement of blood from the trunk to the extremities during maximum-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 recruitment of the expiratory muscles, etc. (Aliverti et al., 2007). Given that EFLe and expiratory loading in general are accompanied by greater intrathoracic pressure swings, cardiac function is also impacted (Cheyne et al., 2020; Stark-Leyva et al., 2004).

The use of EFLe in previous studies allowed valuable information to be gathered 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 for fear of overloading their respiratory system, because 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, because 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 determine the impact of EFLe on blood displacements between body compartments during submaximal exercise and to 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 before data collection. Their anthropometric parameters are shown in Table 1.

Table 1. Participant characteristics and exercise intensity

Parameter	Group	Value
Age (years)		25 ± 3
Height (cm)		177.3 ± 5.4
Weight (kg)		67.4 ± 5.8
$\dot{V}_{O_2max}$ (L min^{-1})		3.671 ± 0.56
$\dot{V}_{O_2}$ Ex3 (L 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

Values are the means ± SD (n = 10). Abbreviations: CTRL, control conditions; EFLe, externally imposed expiratory flow limitation; $\dot{V}_{O_2}$Ex3, oxygen uptake during the final minute of exercise; $\dot{V}_{O_2max}$, absolute peak oxygen uptake; %$\dot{V}_{O_2max}$, percentage of absolute $\dot{V}_{O_2max}$ during the final minute of exercise.

Experimental procedure

The experimental set-up is represented in Fig. 1. Participants sat in a whole-body plethysmography cabin and performed sequences of constant-load submaximal cycling exercise (100 W) for 3 min 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 front wall of the cabin. The EFLe was implemented using a Starling resistor mounted on the expiratory end of a two-way non-rebreathing valve (Hans Rudolph, Shawnee, KS, USA) and restricting expiratory flow to 1 L 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 2 min 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 pedalling 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 r.p.m. Power output was measured by wireless power meter pedals (PowerTap P1; SRAM, Chicago, IL, USA), and participants were guided by a metronome beating at 90 beats min^{-1}.

On another day, participants performed a ramp incremental test on a cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands) to determine maximal oxygen uptake ($\dot{V}_{O_2max}$). After 5 min of warm-up at 1 W kg^{-1}, power output was gradually increased at a rate of 1 W (2 s)$^{-1}$ until participants reached exhaustion. A calibrated metabolic cart (MedGraphics CPX/D; Medical Graphics Corporation, St Paul, MN, USA) monitored oxygen uptake ($\dot{V}_{O_2}$), and $\dot{V}_{O_2max}$ was defined as the highest $\dot{V}_{O_2}$ value reached after averaging breath-by-breath data over 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 and 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 s^{-1}, in a similar manner to previous experiments (Aliverti et al., 2002; Iandelli et al., 2002). Participants were connected to the Starling resistor upon closing the door and throughout the entire exercise sequence, including the resting and recovery periods.

Measurements

During each sequence, a pneumotachograph 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 analyser provided continuous analog signals of airflow and oxygen fraction (F_{O_2}) at the mouth (MedGraphics CPX/D; Medical Graphics Corporation). Eight infrared cameras placed around the cabin tracked the three-dimensional positions of 89 retro-reflective markers taped onto the trunk of the participant to monitor chest wall volume (Vcw) with a three-dimensional calibrated motion analyser (OEP; BTS Bioengineering, Milan, Italy). Two pressure transducers (RCEM250DB; Sensortechnics, Puchheim, Germany), calibrated with a water manometer, measured changes in oesophageal pressure (P_{es}) and gastric pressure (P_{ga}) from balloon-tipped catheters (47-9005; Cooper Surgical, Trumbull, CT, USA) introduced nasally and placed in the oesophagus 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. Oesophageal and gastric balloons were inflated with 1 and 1.5 ml of air, respectively, as recommended by the manufacturer. All signals converged into an analog-to-digital data-acquisition system embedded into the OEP device and were resampled at 60 Hz and time aligned for analysis.

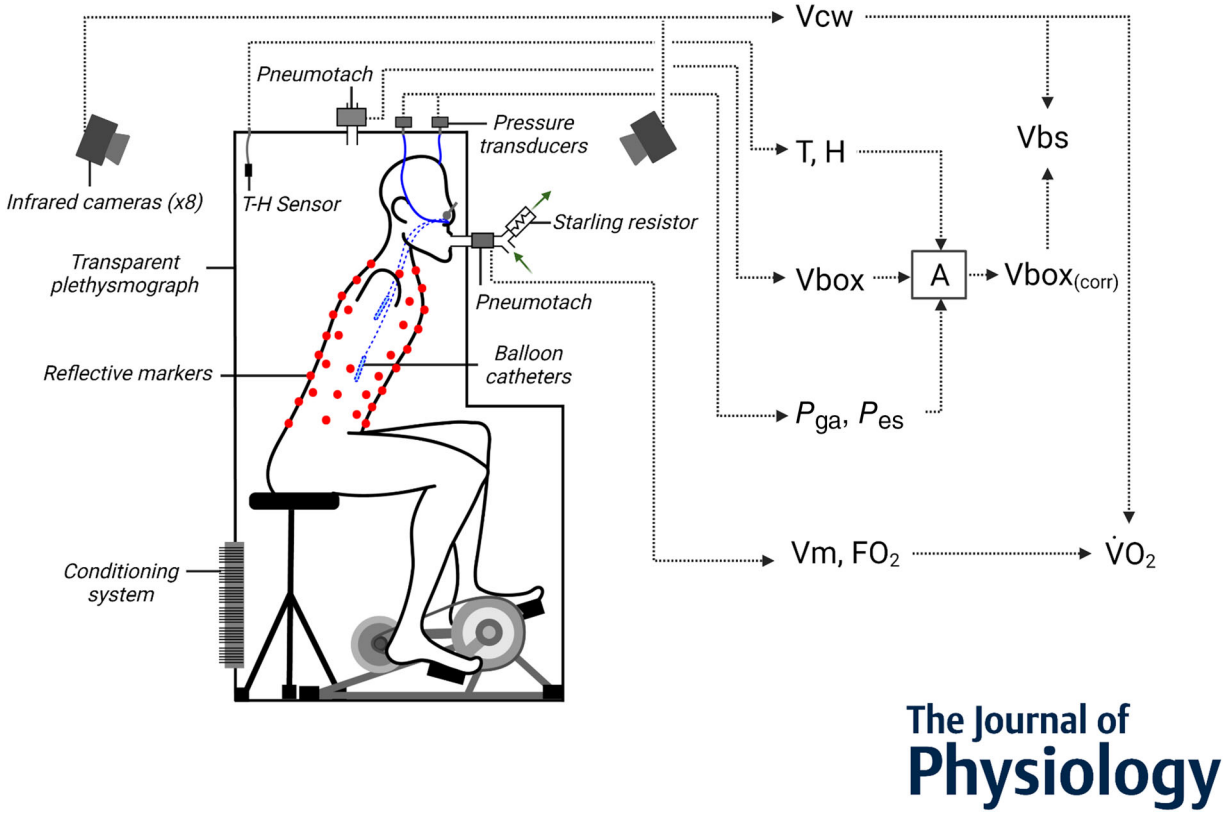

Figure 1. Schematic representation of the experimental set-up
Abbreviations: A, algorithm used to correct Vbox drift; F_{O_2}, O_2 fraction at the mouth; H, humidity; P_{ga}, P_{es}, gastric and oesophageal pressures, respectively; T, temperature; Vbox, volume derived from airflow in and out of the plethysmograph; Vbs, volume of blood shifts; Vcw, chest wall volume; Vm, volume derived from airflow measured at the mouth; $\dot{V}_{O_2}$, oxygen uptake.

Computation of blood shifts. The ΔVb and variations in Vcw (ΔVcw) were collected simultaneously. The ΔVb are attributable to both changes in lung volumes and gas compression and decompression in the lungs, whereas ΔVcw 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 shifting between the trunk and the extremities [volume of blood shift (Vbs)] (Aliverti et al., 2009, 2010; LoMauro & Aliverti, 2018; Stucky et al., 2021; Uva et al., 2016). Before the computation of Vbs, a validated algorithm was used to correct the drift in the ΔVb signal attributable to changes in thermodynamic conditions based on measured values of temperature and humidity and automatically to select the level of a wavelet filter applied to remove the remaining drift in ΔVb attributable to numerical integration of the flow signal (Stucky et al., 2020).

Absolute lung volume. Breath-by-breath absolute lung volume (V_L) could not be estimated directly from the Vcw signal, because the latter also includes the 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 V_L from mathematical integration of airflow measured at the mouth (Vm) and used Vcw to correct the signal for integrator drift and to estimate V_L. 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 their 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 such 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 V_L and the measurement of F_{O_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 approximate alveolar oxygen uptake better (Aliverti, Kayser et al., 2004; Auchincloss et al., 1966).

Data analysis

From the V_L signal, we identified end-inspiratory and end-expiratory points and derived respiratory rate (RR) and tidal volume (V_T). The former was calculated as 60 divided by the duration of each breath (in seconds), whereas the latter was taken as the amplitude between adjacent minimal and maximal V_L values. The product of V_T and RR yielded total minute ventilation ($\dot{V}_E$). Inspiratory time (Tinsp), expiratory time (Texp) and the duty cycle (the ratio between inspiratory time and total breath time) were computed for each breath. The transdiaphragmatic pressure (P_{di}) signal was obtained by offline subtraction of P_{es} from P_{ga}.

To follow the dynamics of the respiratory and haemodynamic variables, each experimental run was divided into six slots of 60 s (Rest, Ex1, Ex2, Ex3, Rec1 and Rec2), over which V_T, RR, $\dot{V}_E$, Texp, Tinsp, duty cycle and $\dot{V}_{O_2}$ signals were averaged. For V_L and Vcw, end-expiratory and end-inspiratory points were averaged separately within each 60 s period, whereas peak expiratory and peak inspiratory values were used for P_{es}, P_{ga}, P_{di} and Vbs. Intrabreath maximal variations of P_{es}, P_{ga} and Vbs were computed breath by breath and averaged over each 60 s 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: (i) the changes in 'operational' Vbs (Vbs,OP) relative to the longer-term variations over the whole exercise sequence compared with quiet breathing; and (ii) the intrabreath Vbs variations (Vbs,I-B). First, breath-by-breath P_{es}, P_{ga} 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 V_L signal. Next, 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 P_{ga} to obtain abdominal pressure (P_{ab}). All signals were then averaged separately during inspiration and expiration. Pearson's correlation coefficients for the relationships P_{es} *vs.* Vbs,OP and P_{ga} *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 P_{es} *vs.* Vbs,I-B and P_{ab} *vs.* Vbs,I-B to examine intrabreath associations.

Statistical analysis

All parameters were compared between conditions (CTRL and EFLe) and across time (Rest, Ex1, Ex2, Ex3, Rec1 and Rec2) using a two-way repeated-measures ANOVA. All pairwise *post hoc* comparisons were performed with the Bonferroni correction. All data are reported as the mean $\pm$ SD. The significance level was set at 0.05. Statistical analyses were performed using SPSS Statistics v.26 (IBM Corporation, Armonk, NY, USA). Associations between the normalized respiratory pressure parameters (P_{es}, P_{ga}, P_{ab} *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 Student's 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 V_T, RR and $\dot{V}_E$ E over time are shown in Fig. 2. In both conditions, RR, V_T and $\dot{V}_E$E increased progressively during exercise and decreased upon recovery. In all phases, RR was decreased with EFLe compared with CTRL. Despite a concurrent increase in V_T, $\dot{V}_E$ remained significantly lower with EFLe at rest and during exercise, whereas it was not significantly different from the CTRL runs during recovery, because 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, although 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. Both Texp and Tinsp were prolonged with EFLe in all phases compared with CTRL, with a greater effect on Texp, as indicated by the systematically lower duty cycle values.

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

Respiratory pressures

Results of the analysis of respiratory pressures are shown in Fig. 5. In both conditions, peak inspiratory P_{es} values decreased gradually with exercise, while peak expiratory values increased gradually. Both were restored progressively to baseline during recovery. In all phases, EFLe resulted in lower peak inspiratory values and higher peak expiratory values compared with CTRL, which produced a systematic increase in the amplitude of intra-breath P_{es} swings. Peak inspiratory P_{ga} remained stable throughout the sequence in both conditions and was elevated with EFLe during exercise and the first minute of recovery. Peak expiratory P_{ga} increased with exercise in both conditions, with values significantly higher with EFLe in all phases. This resulted in greater intra-breath P_{ga} swings with EFLe compared with CTRL. The P_{es} data from one subject had to be excluded owing to aberrant results (positive P_{es} throughout the respiratory cycle), presumably resulting from the displacement of the oesophageal 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 decreased further throughout the 3 min of pedalling, reaching significantly lower values compared with CTRL in all stages of exercise (Fig. 6). This effect was partly reversed during recovery, with a progressive, albeit incomplete, return to baseline values towards the end of the sequence, with values remaining significantly lower compared with CTRL. In addition, the volume of blood shifting between the trunk and the extremities over each breath (i.e. the amplitude of intrabreath Vbs swings) increased at all stages of the sequence with EFLe compared with 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 P_{es} and expiratory P_{ga} were found to be significantly associated with the changes in Vbs,OP during the corresponding phase, and inspiratory P_{es} and

Table 2. Respiratory and haemodynamic parameters averaged over 60 s slots at rest and during exercise and recovery

	Rest			Ex1			Ex2			Ex3			Rec1			Rec2		
Parameter	CTRL	EFLe	*P*-value	CTRL	EFLe	*P*-value	CTRL	EFLe	*P*-value	CTRL	EFLe	*P*-value	CTRL	EFLe	*P*-value	CTRL	EFLe	*P*-value
V_T (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 (breaths 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
$\dot{V}_E$ (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
P_{es} 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
P_{es} 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
P_{ga} 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
P_{ga} 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 (L)	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 ± 0.03	0.3 ± 0.18	<0.001

Abbreviations: CTRL, normal breathing; EFLe, external expiratory flow limitation; EILV, EELV, end-inspiratory and end-expiratory lung volume (relative to functional residual capacity), respectively; Ex1,2,3, average values over the first, second and third minute of exercise; P_{es} peak insp, exp, peak inspiratory and expiratory oesophageal pressure, respectively, P_{ga} = gastric pressure; Rec, recovery; RR, respiratory rate; Texp, expiratory time; Tinsp, inspiratory time; Vbs, volume of blood shift; Vbs swings, intrabreath Vbs amplitude; $\dot{V}_E$, ventilation; V_T, tidal volume.

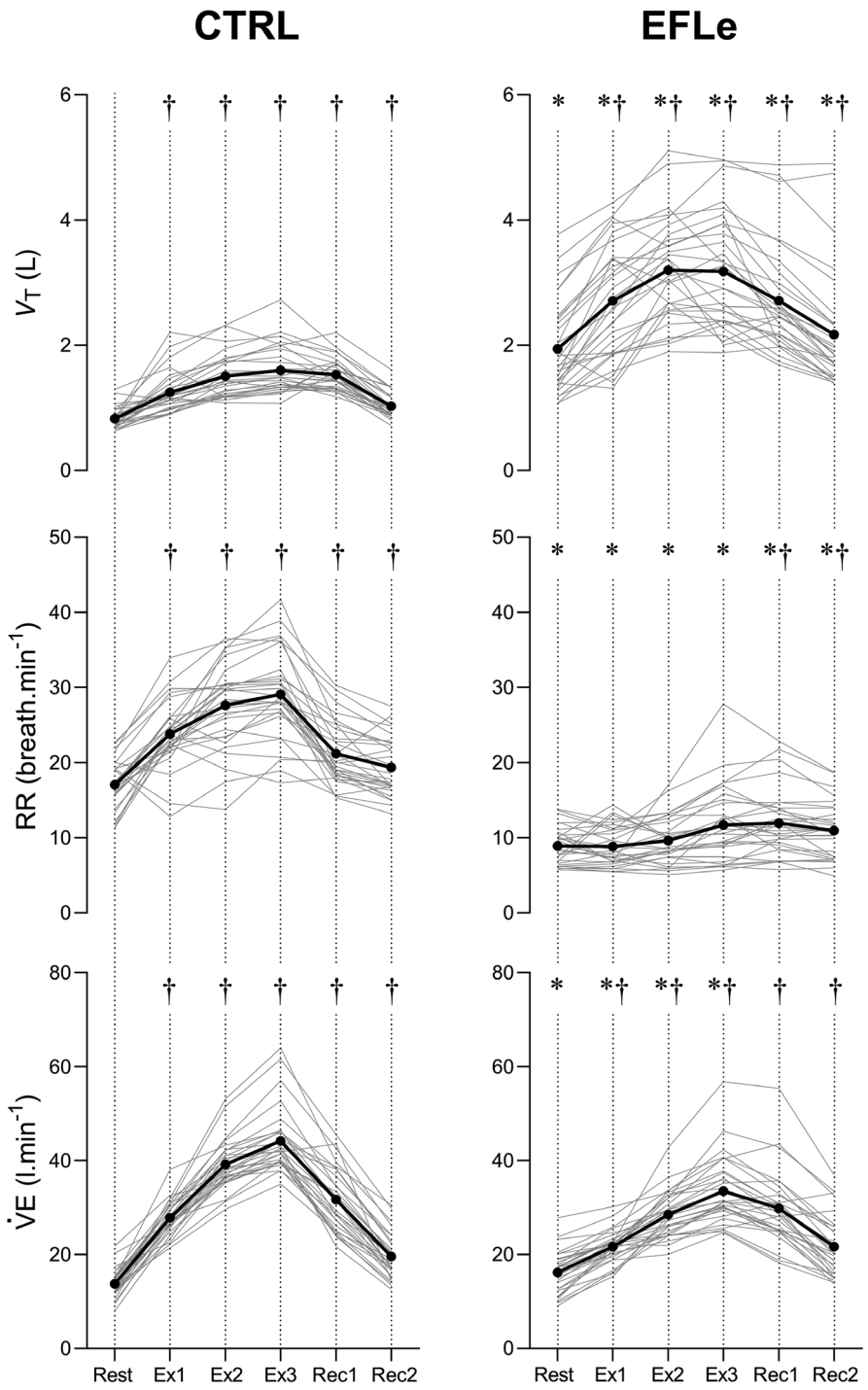

Figure 2. Tidal volume (V_T, top) respiratory rate (RR, middle) and minute ventilation ($\dot{V}_E$, bottom) over time during a sequence of 1 min rest, 3 min of constant-load exercise (Ex1,2,3) and 2 min of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without (CTRL)
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 CTRL; †different from rest ($P < 0.05$). $n = 10$.

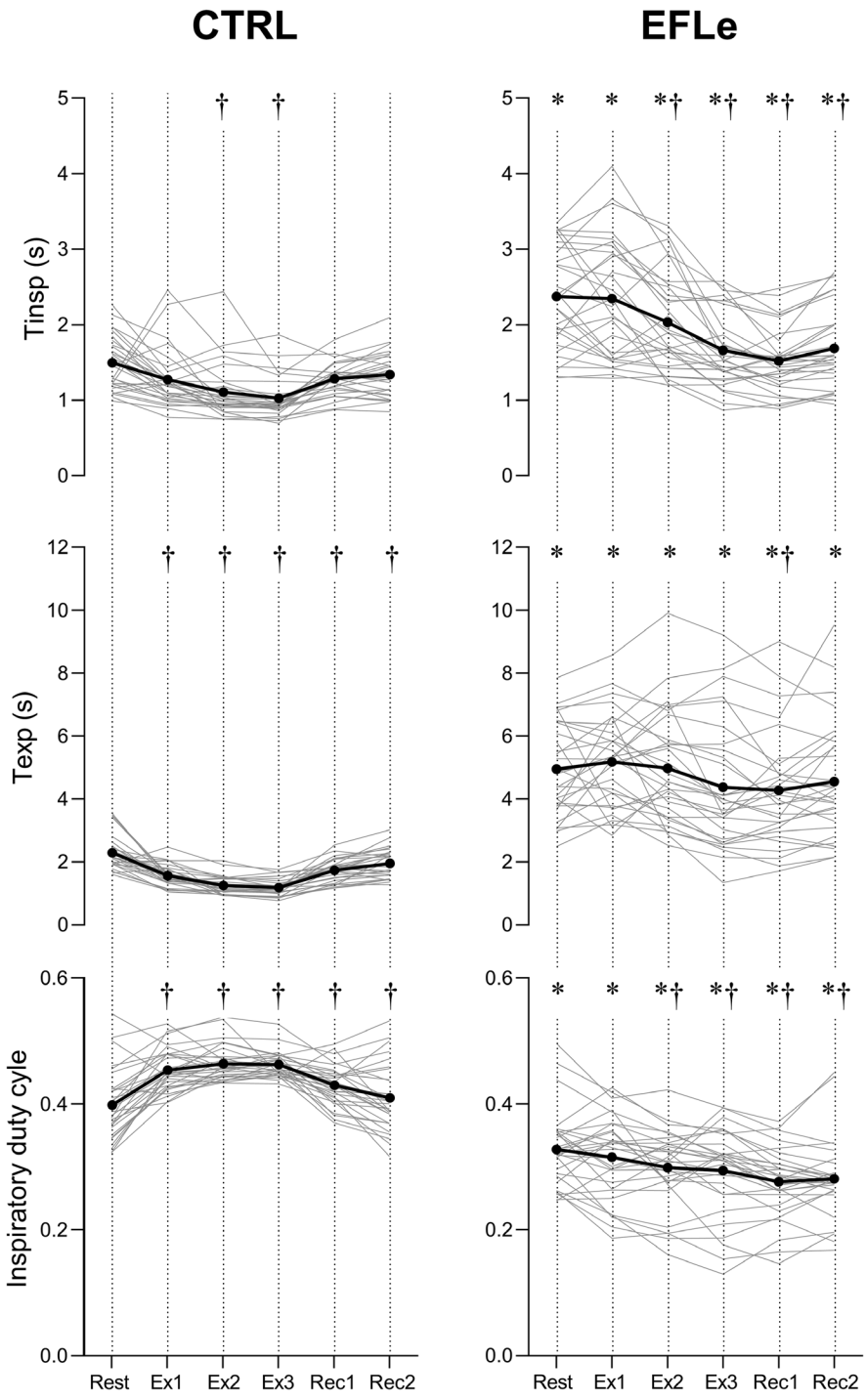

Figure 3. Inspiratory time (Tinsp, top), expiratory time (Texp, middle) and inspiratory duty cycle (Ti/Ttot, bottom) over time during a sequence of 1 min rest, 3 min of constant-load exercise (Ex1,2,3) and 2 min of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without (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 CTRL; †different from rest ($P < 0.05$). $n = 10$.

P_{ab} and expiratory P_{ab} 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 (Dodd et al., 1984; Potter et al., 1971), which was previously reproduced with EFLe in healthy participants (Aliverti et al., 2002; Iandelli et al., 2002; Kayser et al., 1997; 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 muscle shortening (Aliverti et al., 2002). Conversely, EFLe increases inspiratory flow and thus increases the shortening velocity of the inspiratory muscles. Our findings generally concur with these previous reports (Figs 3 and 5). From a mechanical standpoint, the decrease in peak inspiratory P_{es} observed with EFLe implies that inspiratory flow and inspiratory muscle shortening velocity were increased despite the concurrent increase in Tinsp (Fig. 3). This suggests that the increase in inspiratory muscle lengthening amplitude with EFLe was superior in magnitude to the increase in Tinsp. To support this contention, we analysed the increase in the compartmental subdivision of Vcw corresponding to the pulmonary rib cage (Vrcp) and calculated the ratio between the increase in Vrcp and Tinsp. We found an average increase in ΔVrcp/Tinsp of $+61 \pm 22\%$ with EFLe, suggesting that in these conditions the velocity of shortening of the inspiratory muscles was indeed increased compared with the control conditions.

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 (Aliverti et al., 2008; Bauerle et al., 1998; O'Donnell et al., 1997; O'Donnell, 2006). However, the development of dynamic hyperinflation during exercise is not observed systematically in COPD, and different patterns of lung volume dynamics can be identified (Aliverti, Stevenson et al., 2004; Bauerle et al., 1998). 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 with the control conditions (Fig. 4). However, individual traces appeared to follow a range of different patterns. To apprehend this variability, each EFLe run was analysed separately based on the dynamics of EELV. We calculated the mean and SD of all breath-by-breath EELV values at rest during the CTRL runs for each participant and defined an individual threshold zone equal to the mean $\pm$ 4SD. Each EFLe run was then

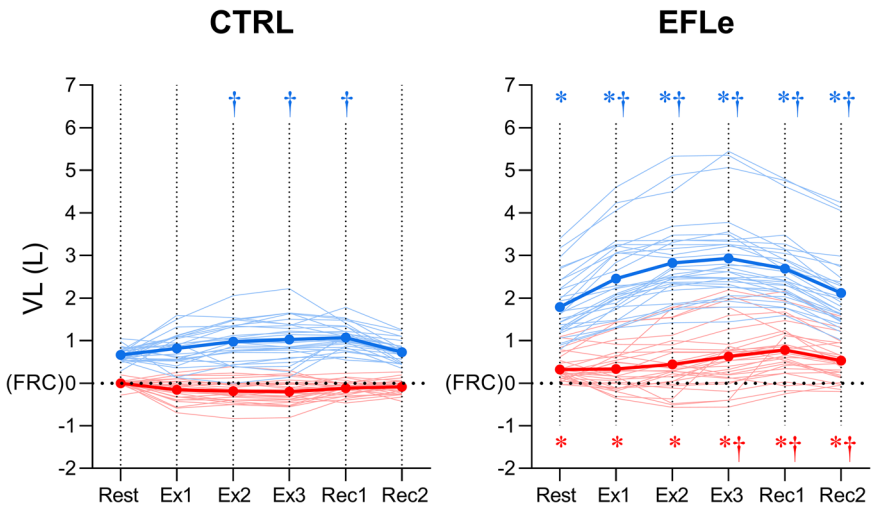

Figure 4. End-inspiratory (blue) and end-expiratory (red) lung volume (V_L) over time during a sequence of 1 min rest, 3 min of constant-load exercise (Ex1,2,3) and 2 min of recovery (Rec1,2) with (EFLe) and without (CTRL)
Values are calculated breath by breath and averaged over each period. Data are reported as variations from functional residual capacity (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 CTRL; †different from rest ($P < 0.05$). $n = 10$.

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% (Fig. 7*A*). In addition, because each participant repeated the same exercise sequence three times, our dataset revealed that not only did dynamic hyperinflation 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

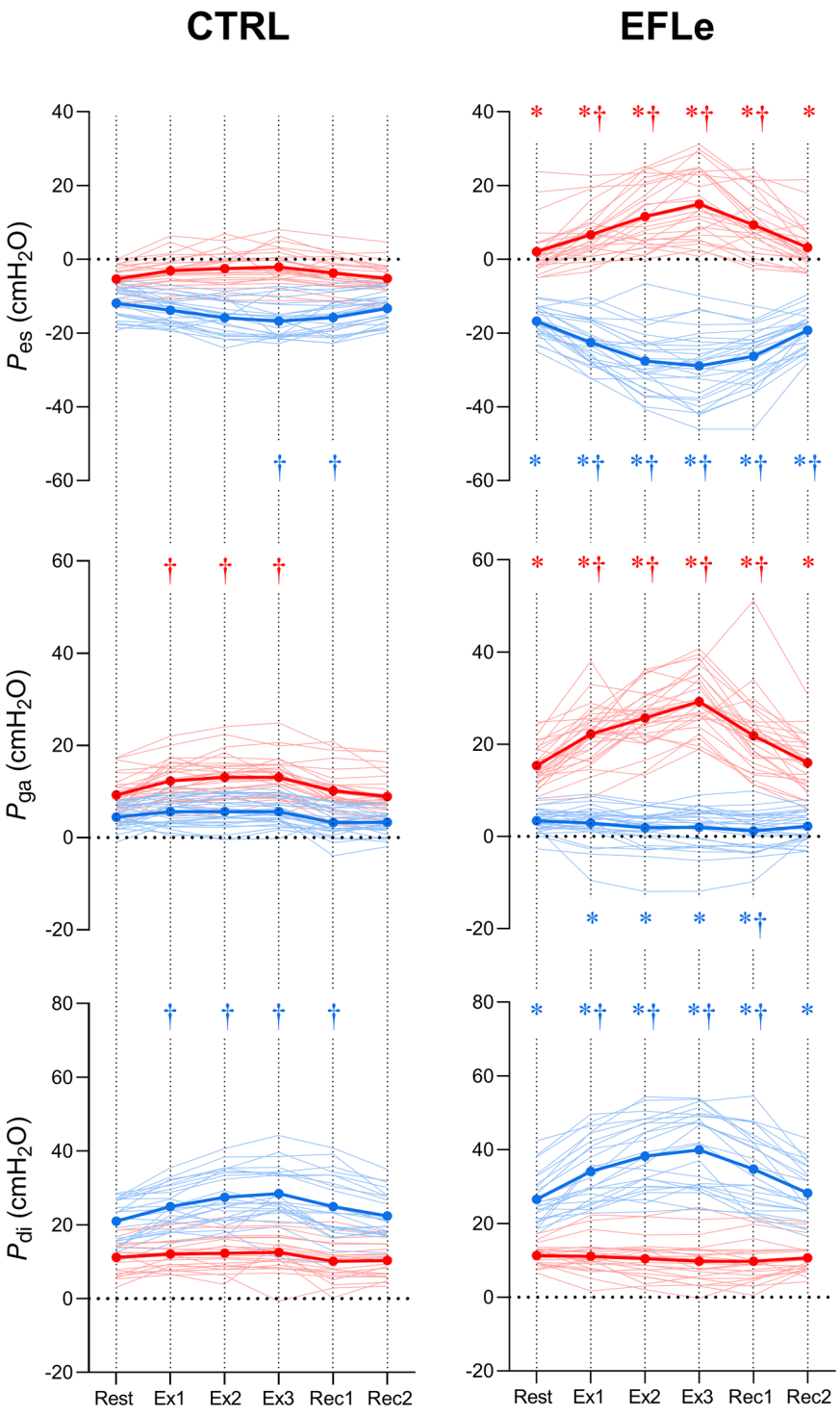

Figure 5. Peak inspiratory (blue) and expiratory (red) oesophageal (P_{es}, top panel), gastric (P_{ga}, middle panel) and transdiaphragmatic (P_{di}, bottom panel) pressure over time during a sequence of 1 min rest, 3 min of constant-load exercise (Ex1,2,3) and 2 min of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without (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 CTRL; †different from rest ($P < 0.05$). $n = 9$.

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

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

Bold text indicated *P*-values < 0.05. Abbreviations: 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; INSP, EXP, average values during inspiration and expiration, respectively; P_{ab}, abdominal pressure; P_{es}, oesophageal pressure; P_{ga}, gastric pressure; Vbs, volume of blood shift; Vbs,I-B, intrabreath variations in Vbs; Vbs,OP, operational Vbs relative to quiet breathing.

observed in a healthy population experiencing EFLe (Aliverti et al., 2002; Iandelli et al., 2002) and in patients with COPD (Aliverti, Stevenson et al., 2004). Specifically, they indicate that different recruitment strategies of respiratory muscles 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 also observed by examining the differences in both the flow–volume loops during exercise and the behaviour

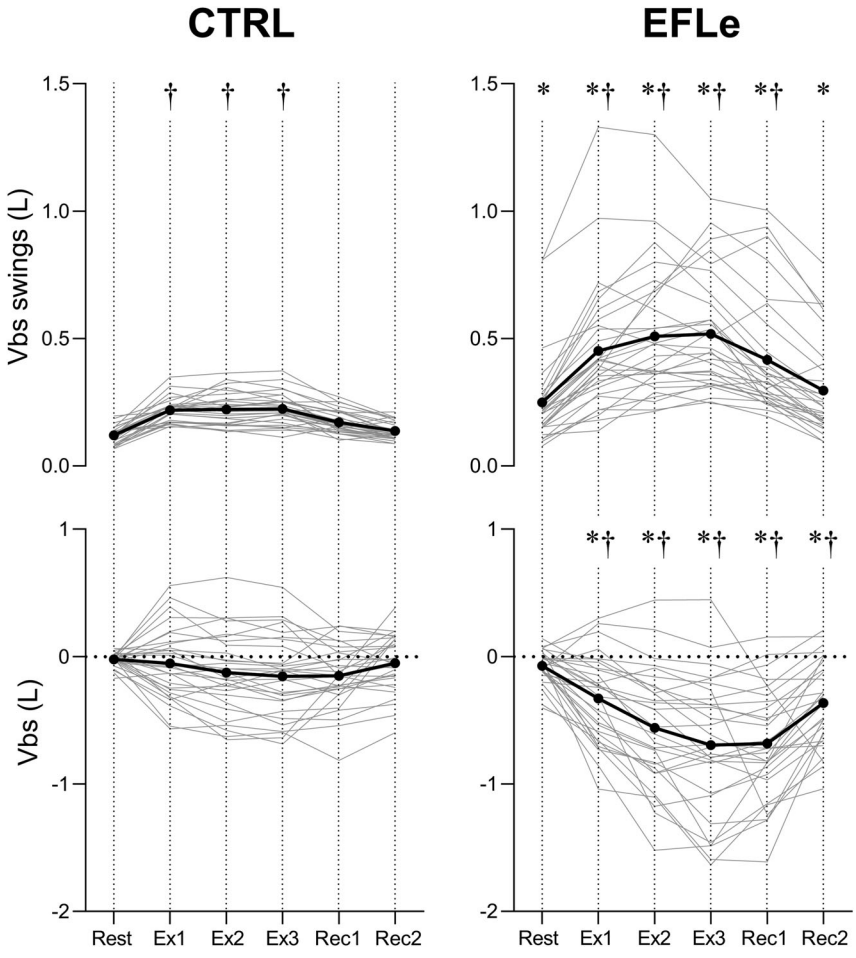

Figure 6. Volume of blood shift (Vbs, bottom panel) and intrabreath Vbs amplitude (Vbs swings, top panel) over time during a sequence of 1 min rest, 3 min of constant-load exercise (Ex1,2,3) and 2 min of recovery (Rec1,2) with externally imposed expiratory flow limitation (EFLe) and without (CTRL)
For 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 CTRL; †different from rest ($P < 0.05$). $n = 10$.

of Tinsp between the three different breathing patterns (Fig. 8). The impact of these differences in breathing mechanics on blood displacements is illustrated in Fig. 7*B* and discussed hereafter.

Blood displacements

The haemodynamic analysis carried out with double body plethysmography in the present study showed that EFLe resulted in larger Vbs swings, indicating an increase in intrabreath blood displacements between the trunk and the extremities (Fig. 6). Moreover, during exercise, Vbs gradually decreased towards negative values, reflecting a net redistribution of blood into the trunk over time. Our measurements of P_{es} and P_{ga} (used as estimates of intrathoracic and intra-abdominal pressure, respectively) can help to provide a mechanistic explanation for these haemodynamic 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) and that a reduction in intrathoracic pressure stimulates venous return by widening the pressure gradient between the peripheral and thoracic circulation (Guyton et al., 1957). These interactions were also confirmed by exacerbating the amplitude of intra-abdominal and intrathoracic pressure variations experimentally with voluntary expulsive manoeuvres (Aliverti et al., 2009, 2010) and inspiratory loading (Cheyne et al., 2016, 2018), respectively. In addition, it was suggested that a greater decrease in intrathoracic pressure could hinder left ventricular stroke volume through direct ventricular interaction (i.e. the increase in right ventricular filling would reduce left ventricular

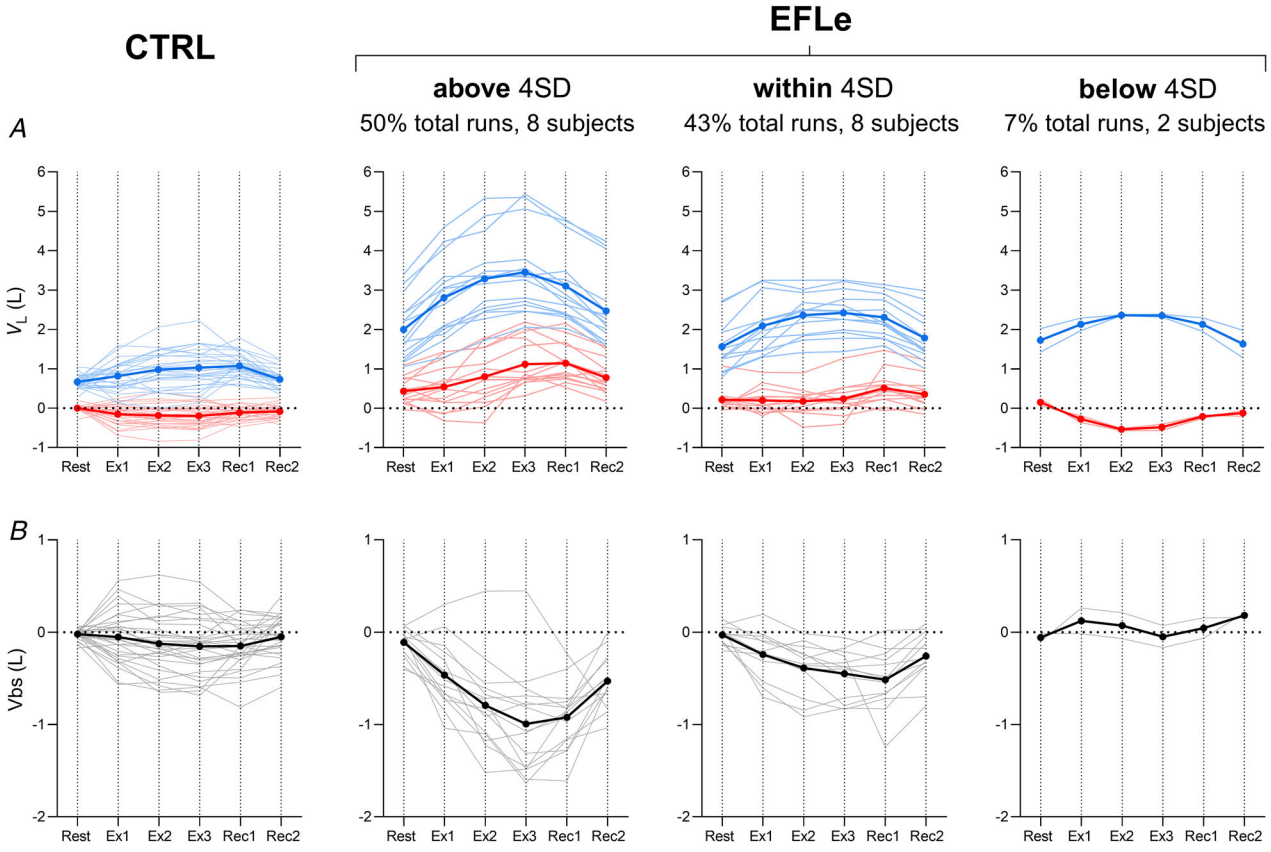

Figure 7. Categorization of externally imposed expiratory flow limitation (EFLe) runs based on observed end-expiratory lung volume (EELV) during the final minute of exercise (Ex3), into those above, within or below the range (4SD) of resting CTRL values
A, classification of end-expiratory lung volume (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) ±4SD for each participant. The 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 (V_L) values, respectively. Individual traces are shown in lighter colours. *B*, volume of blood shift (Vbs) during control conditions (CTRL) and with externally applied expiratory flow limitation (EFLe). The 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.

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 manoeuvres, designed to increase intra-abdominal and intrathoracic pressure swings selectively by emphasizing the action of the diaphragm and the rib cage muscles, respectively, resulted in an increase in Vbs swings compared with spontaneous breathing (Stucky et al., 2021; Uva et al., 2016).

In the present 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 (Fig. 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 (Fig. 6). Yet, it was previously hypothesized that the development of high expiratory pressures with EFLe would act like a Valsalva manoeuvre and thus decrease venous return and cardiac output (Aliverti et al., 2005; Iandelli et al., 2002; Potter et al., 1971). Indeed, increasing intra-abdominal pressure beyond a certain level can lead to a momentary halting of femoral venous return owing to the consequent decrease in the pressure gradient between the thorax and the periphery (Miller et al. 2005a, b). Although it is certainly possible that the EFLe-driven increase in intra-abdominal and intrathoracic pressures 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; Fig. 9). Indeed, we found that the intrabreath Vbs variations were positively associated with P_{es} during inspiration and with P_{ab} during expiration, confirming that the alternation between lower inspiratory intrathoracic and higher expiratory intra-abdominal pressure values plays a role in the increase in intra-breath Vbs swings with EFLe. Further analyses revealed that the relationship between intrabreath Vbs and P_{es} during inspiration could be described better using an

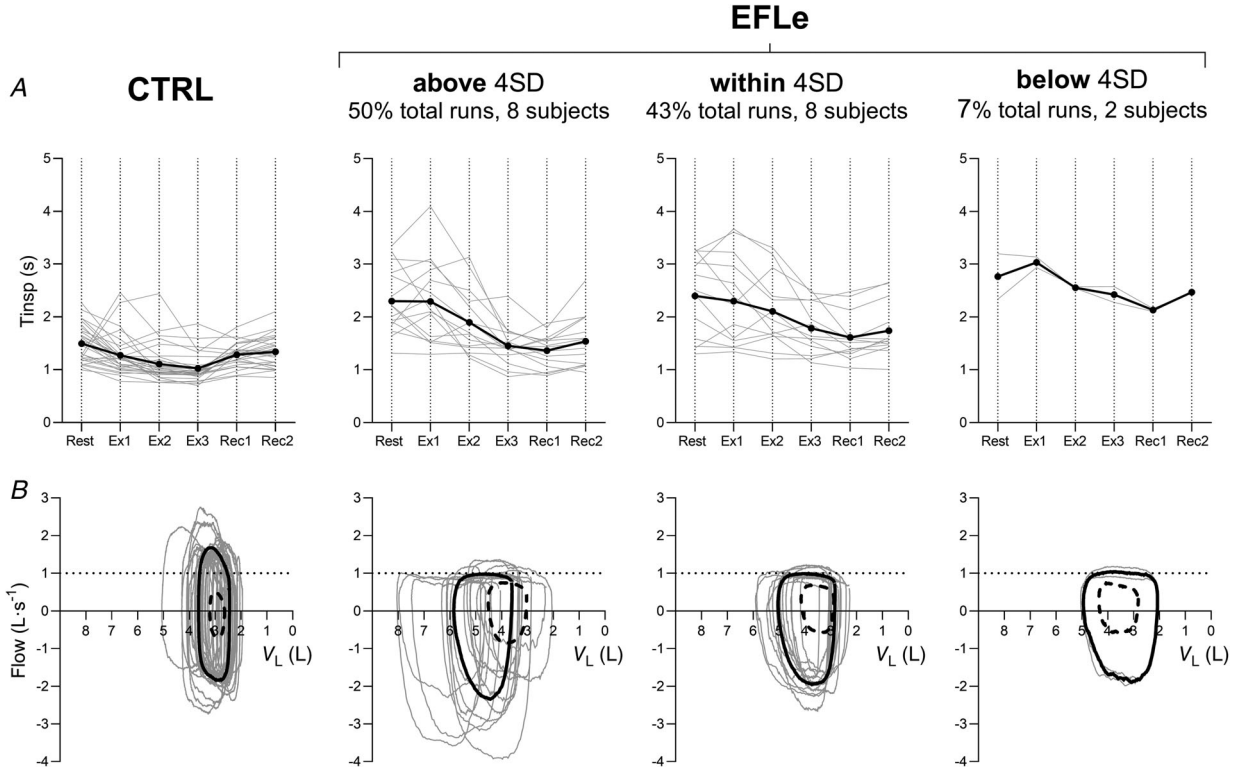

Figure 8. Inspiratory time (Tinsp) and flow-volume loops during control conditions (CTRL) and externally imposed expiratory flow limitation (EFLe) runs in the three different categories defined accordingly to observed end-expiratory lung volume (EELV) during the final minute of exercise (Ex3) (see Fig. 7)
A, inspiratory time (Tinsp) traces during control conditions (CTRL) and with induced expiratory flow limitation (EFLe), categorized according to the pattern followed by end-expiratory lung volume during exercise. *B*, corresponding flow–volume loops at rest (dashed lines) and during the last minute of exercise (Ex3, continuous lines). $n = 10$.

exponential function rather than a linear regression (R^2 = 0.408 *vs.* 0.292, respectively; Fig. 9*B*). From a physiological standpoint, the use of an exponential model implies that average inspiratory P_{es} must drop below a certain level to produce a detectable displacement of blood into the trunk effectively. Thus, assuming a 'detection' threshold value of 50 ml for intrabreath Vbs (Aliverti et al., 2009, 2010), our data show that this critical average P_{es} value throughout inspiration would be located around −14 cmH_2O (Fig. 7*B*). In addition to the intrabreath effect of respiratory pressures, the reduction in operational Vbs compared with baseline over time was positively associated with inspiratory P_{es}, but negatively associated with expiratory P_{ga}. These results suggest that the lower intrathoracic 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 reductions in intrathoracic pressure, drawing blood from the peripheral circulation. This phenomenon is also illustrated by the qualitative differences in Vbs patterns, where the decrease in operational Vbs was more pronounced during the 'hyperinflator' runs, in which P_{es} decreased more drastically owing to greater end-inspiratory lung volume (EILV) levels (Fig. 7). As hypothesized in previous experiments, this inflow of blood into the trunk from the extremities might be accommodated, in part, by the recruitment of the low-resistance and high-capacitance pulmonary vascular system (Flamm et al., 1990).

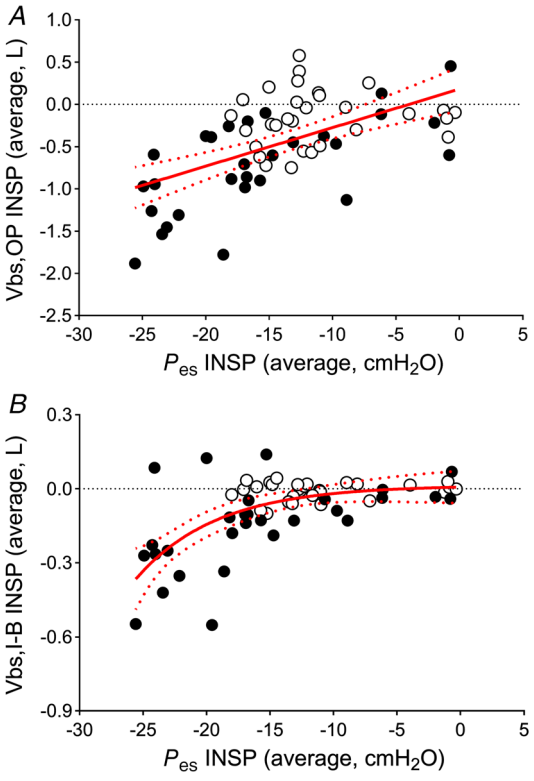

Figure 9. Relationship between mean values of oesophageal pressure (P_{es}) and operational volume of blood shift (Vbs,OP; *A*) or intrabreath blood shifts (Vbs,I-B; *B*) during inspiration within the last minute of exercise
Data points are represented during spontaneous breathing (open circles) and externally imposed expiratory flow limitation (filled circles). Continuous red lines are linear (*A*) and exponential (*B*) regressions; dotted red lines are 95% confidence bands. n = 9.

Previous experiments associated the development of high expiratory pressure in EFLe with a reduction in venous return (Aliverti et al., 2005; Iandelli et al., 2002; Potter et al., 1971; Stark-Leyva et al., 2004) 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 haemodynamic effect of EFLe might differ according to the intensity of exercise. At maximal intensity, it is 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 P_{ga} and P_{es} at maximal intensity, respectively, whereas our estimations during the final minute of submaximal exercise amounted to only 29.2 ± 6.1 and 13.2 ± 10.5 cmH_2O, respectively (Fig. 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 evident in only 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 V_T and limit hypoventilation. Finally, the submaximal intensity used in our protocol (corresponding to ∼40% of $\dot{V}_{O_2max}$) was sufficiently low to enable Tinsp to increase with EFLe compared with CTRL, whereas a systematic decrease in Tinsp was previously reported at maximal intensity (Aliverti et al., 2005; Iandelli et al., 2002; Kayser et al., 1997). In our study, although the duty cycle decreased substantially because of the more pronounced increase in Texp, the increase in Tinsp might have been just sufficient to allow the inspiratory inflow of blood into the trunk to override the expiratory outflow.

Relevance to COPD

The unique set-up used in the present study enabled us, 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 associated specifically 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 regard 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 haemodynamics and including some inspiratory limitation (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 had above-average aerobic capacity (Table 1), whose cardiovascular properties would be likely to differ substantially 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, polycythaemia 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 haemodynamic 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 that 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 biological sex. Inclusion of women would have necessitated increasing the number of participants included in order to allow comparison, because 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 and greater efficiency in women; 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 set-up, 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, potentially, have reduced experimental noise. Finally, in our calculations of V_L we used age, sex and size estimates of FRC instead of measured values.

Conclusion

Our findings indicate that during submaximal exercise, EFLe produced greater intrabreath 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 intrathoracic pressure during expiration and decrease in intrathoracic 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 the submaximal level. Whether these results can be replicated in COPD patients is unclear and remains to be determined.

References

Alexander, R. S. (1951). Influence of the diaphragm upon portal blood flow and venous return. *American Journal of Physiology*, **167**(3), 738–748.

Aliverti, A., Bovio, D., Fullin, I., Dellacà, R. L., Lo Mauro, A., Pedotti, A., & Macklem, P. T. (2009). The abdominal circulatory pump. *Plos One*, **4**(5), e5550.

Aliverti, A., Dellacà, R. L., Lotti, P., Bertini, S., Duranti, R., Scano, G., Heyman, J., lo Mauro, A., Pedotti, A., & Macklem, P. T. (2005). Influence of expiratory flow-limitation during exercise on systemic oxygen delivery in humans. *European Journal of Applied Physiology*, **95**(2–3), 229–242.

Aliverti, A., Iandelli, I., Duranti, R., Cala, S. J., Kayser, B., Kelly, S., Misuri, G., Pedotti, A., Scano, G., Sliwinski, P., Yan, S., & Macklem, P. T. (2002). Respiratory muscle dynamics and control during exercise with externally imposed expiratory flow limitation. *Journal of Applied Physiology*, **92**(5), 1953–1963.

Aliverti, A., Kayser, B., & Macklem, P. T. (2004). Breath-by-breath assessment of alveolar gas stores and exchange. *Journal of Applied Physiology*, **96**(4), 1464–1469.

Aliverti, A., Kayser, B., & Macklem, P. T. (2007). A human model of the pathophysiology of chronic obstructive pulmonary disease. *Respirology (Carlton, Vic)*, **12**(4), 478–485.

Aliverti, A., Macklem, P. T., Debigaré, R., Maltais, F., O'Donnell, D. E., & Webb, K. A. (2008). Point:Counterpoint: The major limitation to exercise performance in COPD is: 1 inadequate energy supply to the respiratory and locomotor muscles, 2 lower limb muscle dysfunction, 3 dynamic hyperinflation. *Journal of Applied Physiology*, **105**(2), 749–751.

Aliverti, A., Stevenson, N., Dellacà, R. L., lo Mauro, A., Pedotti, A., & Calverley, P. M. A. (2004). Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. *Thorax*, **59**(3), 210–216.

Aliverti, A., Uva, B., Laviola, M., Bovio, D., lo M. A., Tarperi, C., Colombo, E., Loomas, B., Pedotti, A., Similowski, T., & Macklem, P. T. (2010). Concomitant ventilatory and circulatory functions of the diaphragm and abdominal muscles. *Journal of Applied Physiology*, **109**(5), 1432–1440.

Auchincloss, J. H., Gilbert, R., & Baule, G. H. (1966). Effect of ventilation on oxygen transfer during early exercise. *Journal of Applied Physiology*, **21**(3), 810–818.

Bauerle, O., Chrusch, C. A., & Younes, M. (1998). Mechanisms by which COPD affects exercise tolerance. *American Journal of Respiratory and Critical Care Medicine*, **157**(1), 57–68.

Cavaillès, A., Brinchault-Rabin, G., Dixmier, A., Goupil, F., Gut-Gobert, C., Marchand-Adam, S., Meurice, J. C., Morel, H., Person-Tacnet, C., Leroyer, C., & Diot, P. (2013). Comorbidities of COPD. *European Respiratory Review*, **22**(130), 454–475.

Cheyne, W. S., Gelinas, J. C., & Eves, N. D. (2018). The haemodynamic response to incremental increases in negative intrathoracic pressure in healthy humans. *Experimental Physiology*, **103**(4), 581–589.

Cheyne, W. S., Harper, M. I., Gelinas, J. C., Sasso, J. P., & Eves, N. D. (2020). Mechanical cardiopulmonary interactions during exercise in health and disease. *Journal of Applied Physiology*, **128**(5), 1271–1279.

Cheyne, W. S., Williams, A. M., Harper, M. I., & Eves, N. D. (2016). Heart-lung interaction in a model of COPD: Importance of lung volume and direct ventricular interaction. *American Journal of Physiology - Heart and Circulatory Physiology*, **311**(6), H1367–H1374.

Dodd, D. S., Brancatisano, T., & Engel, L. A. (1984). Chest wall mechanics during exercise in patients with severe chronic air-flow obstruction. *American Review of Respiratory Disease*, **129**, 33–38.

Dominelli, P. B., & Molgat-Seon, Y. (2022). Sex, gender and the pulmonary physiology of exercise. *European Respiratory Review*, **31**(163), 210074.

Flamm, S. D., Taki, J., Moore, R., Lewis, S. F., Keech, F., Maltais, F., Ahmad, M., Callahan, R., Dragotakes, S., Alpert, N., & Strauss, H. W. (1990). Redistribution of regional and organ blood volume and effect on cardiac function in relation to upright exercise intensity in healthy human subjects. *Circulation*, **81**(5), 1550–1559.

Guyton, A. C., Lindsey, A. W., Abernathy, B., & Richardson, T. (1957). Venous return at various right atrial pressures and the normal venous return curve. *American Journal of Physiology*, **189**(3), 609–615.

Iandelli, I., Aliverti, A., Kayser, B., Dellacà, R., Cala, S. J., Duranti, R., Kelly, S., Scano, G., Sliwinski, P., Yan, S., Macklem, P. T., & Pedotti, A. (2002). Determinants of exercise performance in normal men with externally imposed expiratory flow limitation. *Journal of Applied Physiology*, **92**(5), 1943–1952.

Kayser, B., Sliwinski, P., Yan, S., Tobiasz, M., & Macklem, P. T. (1997). Respiratory effort sensation during exercise with induced expiratory- flow limitation in healthy humans. *Journal of Applied Physiology*, **83**(3), 936–947.

LoMauro, A., & Aliverti, A. (2018). Blood shift during cough: Negligible or significant? *Frontiers in Physiology*, **9**, 501.

Macklem, P. T. (2005). Exercise in COPD: Damned if you do and damned if you don't. *Thorax*, **60**(11), 887–888.

Miller, J. D., Pegelow, D. F., Jacques, A. J., & Dempsey, J. A. (2005a). Skeletal muscle pump versus respiratory muscle pump: Modulation of venous return from the locomotor limb in humans. *Journal of Physiology*, **563**(3), 925–943.

Miller, J. D., Pegelow, D. F., Jacques, A. J., & Dempsey, J. A. (2005b). Effects of augmented respiratory muscle pressure production on locomotor limb venous return during calf contraction exercise. *Journal of Applied Physiology*, **99**(5), 1802–1815.

O'Donnell, D. E. (2006). Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. In *Proceedings of the American Thoracic Society*, pp. 180–184.

O'Donnell, D. E., Bertley, J. C., Chau, L. K. L., & Webb, K. A. (1997). Qualitative aspects of exertional breathlessness in chronic airflow limitation: Pathophysiologic mechanisms. *American Journal of Respiratory and Critical Care Medicine*, **155**(1), 109–115.

O'Donnell, D. E., James, M. D., Milne, K. M., & Neder, J. A. (2019). The pathophysiology of dyspnea and exercise intolerance in chronic obstructive pulmonary disease. *Clinics in Chest Medicine*, **40**(2), 343–366.

O'Donnell, D. E., & Webb, K. A. (1993). Exertional breathlessness in patients with chronic airflow limitation: The role of lung hyperinflation. *American Review of Respiratory Disease*, **148**(5), 1351–1357.

Potter, W. A., Olafsson, S., & Hyatt, R. E. (1971). Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease. *Journal of Clinical Investigation*, **50**(4), 910–919.

Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R., & Yernault, J. C. (1993). Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. *European Respiratory Journal Supplement*, **6**(Suppl 16), 5–40.

Shujaat, A., Minkin, R., & Eden, E. (2007). Pulmonary hypertension and chronic cor pulmonale in COPD. *International Journal of COPD*, **2**, 273–282.

Stark-Leyva, K. N., Beck, K. C., & Johnson, B. D. (2004). Influence of expiratory loading and hyperinflation on cardiac output during exercise. *Journal of Applied Physiology*, **96**(5), 1920–1927.

Stucky, F., Aliverti, A., Kayser, B., & Uva, B. (2021). Priming the cardiodynamic phase of pulmonary oxygen uptake through voluntary modulations of the respiratory pump at the onset of exercise. *Experimental Physiology*, **106**(2), 555–566.

Stucky, F., Cazzaniga, G., Aliverti, A., Kayser, B., & Uva, B. (2020). Automating the correction of flow integration drift during whole-body plethysmography. In *2020 42nd Annual International Conference of the IEEE Engineering in Medicine Biology Society (EMBC)*, pp. 5–8.

Takata, M., Wise, R. A., & Robotham, J. L. (1990). Effects of abdominal pressure on venous return: Abdominal vascular zone conditions. *Journal of Applied Physiology*, **69**(6), 1961–1972.

Uva, B., Aliverti, A., Bovio, D., & Kayser, B. (2016). The "Abdominal Circulatory Pump": An auxiliary heart during exercise? *Frontiers in Physiology*, **6**, 1–12.

Wheatley, C. M., Snyder, E. M., Johnson, B. D., & Olson, T. P. (2014). Sex differences in cardiovascular function during submaximal exercise in humans. *Springerplus*, **3**(1), 1–13.

Additional information

Data availability statement

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

Competing interests

None.

Author 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 the manuscript and critical revision: F.S., B.U., A.A. and B.K. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Statistical Summary Document
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