Influence of expiratory loading and hyperinflation on cardiac output during exercise

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STARK-LEYVA, Kristy N., Ken C. Beck, and Bruce D. Johnson. Influence of expiratory loading and hyperinflation on cardiac output during exercise. J Appl Physiol 96: 1920–1927, 2004.—Patients with obstructive lung disease are exposed to expiratory loads (ELs) and dynamic hyperinflation as a consequence of expiratory flow limitation. To understand how these alterations in lung mechanics might affect cardiac function, we examined the influence of a 10-cmH2O EL, alone and in combination with voluntary hyperinflation (ELH), on pulmonary pressures [esophageal (Pes) and gastric (Pg)] and cardiac output (CO) in seven healthy subjects. CO was determined by using an acetylene method at rest and at 40 and 70% of peak work. At rest and during exercise, EL resulted in an increase in Pes and Pg (7–18 cmH2O; P < 0.05) and a decrease in CO (from 5.3 ± 1.8 to 4.5 ± 1.4, 12.2 ± 2.2 to 11.2 ± 2.2, and 16.3 ± 3.3 to 15.2 ± 3.2 l/min for rest, 40% peak work, and 70% peak work, respectively; P < 0.05), which remained depressed after an additional 2 min of EL. With ELH, CO increased at rest and both exercise loads (relative to EL only) but remained below control values. The changes in CO were due to a reduction in stroke volume with a tendency for stroke volume to fall further with prolonged EL. There was a negative correlation between CO and the increase in expiratory Pes and Pg with EL (R = −0.58 and −0.60; P < 0.01), whereas the rise in CO with subsequent hyperinflation was related to a more negative Pes (R = 0.72; P < 0.01). In conclusion, EL leads to a reduction in CO, which appears to be primarily related to increases in expiratory abdominal and intrathoracic pressure, whereas ELH resulted in an improved CO, suggesting that lung inflation has little impact on cardiac function.

FACTORS THAT INFLUENCE EXERCISE TOLERANCE in patients with obstructive lung disease remain controversial (3, 10, 21, 22, 24). Although reduced lung function clearly plays a significant and initiating role, several studies (21, 24) have suggested that cardiac function may play a more dominant role in limiting exercise capacity in more severe lung disease. A study by Montes de Oca et al. (21) found oxygen pulse [oxygen consumption (VO2)/heart rate (HR)] measured during exercise to be the best predictor of peak VO2 in patients with an average forced expiratory volume in 1 s of 0.79 liter. Oelberg et al. (23) found a blunted cardiac output (CO) during exercise in patients with chronic obstructive pulmonary disease (COPD) relative to normal subjects. These studies suggest that cardiac function may be altered during exercise in COPD patients; however, the degree to which cardiac function is influenced by lung mechanics is not clear.

During activity, patients with obstructive lung disease experience increased expiratory loads (ELs) as well as progressive hyperinflation [gradual rise in end-expiratory lung volume (EELV)] as ventilatory demand increases, both of which are secondary to expiratory airflow limitation (22, 24). Studies have suggested that, in the resting state, ELs created by positive-pressure breathing reduce CO, likely via an effect of increasing pleural pressure and right atrial pressure, and subsequently reducing venous return (5, 19, 28). However, during exercise with large negative swings in pleural pressure, alterations in abdominal pressure (Pg), changes in lung volume (both the tidal swings and the EELV), and alterations in venous return due to contraction of limb muscles (29, 34), the impact of expiratory loading on cardiac function is less clear (24).

The separate influence of dynamic hyperinflation combined with increases in tidal volume (VT) on CO is also unclear (16). Because the heart and lungs share a common surface area, a progressive lung inflation with exercise may increase competition for intrathoracic space and inhibit cardiac filling via a change in cardiac compliance (25). Interestingly, in a previous study involving exercise with chest wall restriction (20), the decline in CO appeared to more closely parallel alterations in gastric and intrathoracic pressure (Pe) rather than the changes in lung volume. Thus the impact of changes in lung inflation on CO, particularly during exercise, is uncertain.

The purpose of the present investigation was to more clearly determine the influence of a modest EL (10 cmH2O) alone and in combination with voluntary hyperinflation (ELH) on pulmonary mechanics and cardiac function during light and moderate exercise in healthy subjects. We hypothesized that the increases in Pe and Pg with expiratory loading would transiently reduce CO and that the pressure changes with loading would be more important than lung volume changes (hyperinflation) in decreasing CO.

METHODS

Subjects. All aspects of the study were approved by the Mayo Clinic Institutional Review Board. Volunteers were recruited from the local area. Seven healthy subjects (4 men, 3 women) without a history of cardiac or respiratory problems (nonsmokers), aged 22–53 yr, and with a variety of activity levels gave written, informed consent before participation.

Exercise protocol. Subjects reported to the General Clinical Research Center Exercise Core Laboratory on two occasions. The first visit consisted of an incremental cycle ergometry test to determine peak VO2 and peak work level (Wpeak). The second visit consisted of measurements of CO and lung mechanics at rest and during steady-
state exercise (at 40 and 70% W\textsubscript{peak} achieved on the initial visit) while exposed to a 10-cm\textsubscript{H2O} EL or ELH. A 10-cm\textsubscript{H2O} load was chosen to mimic the physiological loads presented to patients with COPD, particularly during exercise when expiratory flow limitation is present (24).

**Visit 1.** Before exercise, subjects were instrumented with a 12-lead ECG and blood pressure cuff. After 5 min of light cycling and stretching, the subject began a progressive cycle ergometry test. This test involved pedaling at an initial workload of 20–35 W for 1 min, with workload increases of 20–35 W every minute thereafter until volitional fatigue. Measurements of HR and blood pressure were assessed at the conclusion of each work level, while gas-exchange measurements (\(\dot{V}O_2, \dot{CO}_2\) production, and minute ventilation) were assessed continuously.

**Visit 2.** In addition to the 12-lead ECG, gastric and esophageal balloons were placed intranasally (see *Pulmonary mechanics* below). For assessment of CO and pulmonary mechanics, subjects breathed through a low-resistance mouthpiece attached in series to a pneumotachograph mounted at a comfortable height. This height was held constant throughout testing to minimize the effect of posture changes on the pulmonary function testing. For each subject, measurements of cardiac function (CO and HR) and lung mechanics (lung volume, pulmonary pressures, and flow) were collected at rest and at 40 and 70% W\textsubscript{peak}. At each workload, measurements were made under the following sequence of conditions: 1) normal breathing [control (CTL) conditions], 2) normal breathing (repeat CTL conditions), 3) breathing against an EL, and 4) breathing against an ELH. During the 40 and 70% W\textsubscript{peak} intensities, measurements were made at various work levels.

**Expiratory loading and voluntary hyperinflation.** The EL was created using a proportional assist ventilator (Respironics, model no. PE200) and was applied for 10 breaths and does not require a rebreathing or alterations in breathing pattern on the part of the subject. Although the increased pressure on expiration could in principle require the wash-in of acetylene gas mixture (0.6% C\textsubscript{2}H\textsubscript{2}, 1% increase in O\textsubscript{2} of 106%–93% of predicted) and reach an average peak V\textsubscript{O\textsubscript{2} of 106 ± 22% of the age predicted value. MAP increased by 15 mmHg from rest to peak exercise (\(P < 0.05\)), due entirely to a rise in SBP.

**Constant-load exercise.** For each subject at rest, none of the cardiac- or breathing-related variables differed between the two CTL conditions, and the data were averaged for comparison with EL and ELH. During exercise at the 40 and 70% work levels, respiratory variables did not significantly differ from the baseline values. Airflow was determined simultaneously with the pressure measurements, and volume was obtained by the digital integration of the linearized flow signal (35), corrected for drift (unequal inspiration to expiration over time), using a computer program developed in our laboratory (2).

**Data analysis.** For rest and each level of exercise, measurements of cardiac function and pulmonary mechanics were collected immediately after the onset of EL and in the last 30 s of each condition (CTL conditions, EL, and ELH). Cardiovascular variables included HR, CO, and systolic (SBP) and diastolic blood pressure (DBP). Mean arterial pressure (MAP) was calculated as (SBP − DBP)/3 + DBP. Respiratory variables included end-tidal CO\textsubscript{2} (PET\textsubscript{CO\textsubscript{2}}), \(V_t\), breathing frequency (f), inspiratory capacity (IC), inspiratory time (TI) as a percentage of the total breathing cycle (TI/TTot), and end-inspiratory (EI) index [EI index = (ERV + \(V_t\))/VC], where ERV is the expiratory reserve volume and VC is the vital capacity. The IC was used to follow changes in EELV under the three conditions, whereas EL index was used as an index of the degree of lung inflation relative to the full inflation volume (in this case, VC). Continuous measurements of Pe and Pg were obtained throughout the breathing cycle under the various conditions. From these measurements, tidal Pe- and Pg-volume loops were plotted relative to the IC determined EELVs (17). In addition, peak changes in Pe and Pg were recorded along with the integrated pressures over the course of each breath, both for inspiration and expiration. Mean Pe and Pg time integrals for the entire breathing cycle were divided by the mean TI and expiratory time (Te) to determine mean shifts in Pe and Pg with EL and ELH (17, 20). Differences between EL and CTL, ELH and CTL, and EL and ELH conditions were assessed by first applying ANOVA to test the hypothesis that there was a difference among the conditions, correcting for a time effect using a continuous time variable. Because ANOVA indicated a significant effect, we applied paired t-tests between conditions of interest (CTL vs. EL, CTL vs. ELH, and EL vs. ELH) for rest and each exercise level, with \(P < 0.05\) suggesting significance.

**RESULTS**

**Incremental exercise.** Subject characteristics and peak exercise values are shown in Table 1. During the initial incremental study to define W\textsubscript{peak}, subjects achieved 91 ± 15% of their age-predicted maximum HR (range 87–93% of predicted) and reached an average peak \(\dot{V}O_2\) of 106 ± 22% of the age predicted value. MAP increased by 15 mmHg from rest to peak exercise (\(P < 0.05\)), due entirely to a rise in SBP.

**Table 1. Subject characteristics and peak exercise data**

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>FEV\textsubscript{1}, % predicted</th>
<th>V\textsubscript{O\textsubscript{2}}, ml/kg \textsubscript{HR} \textsuperscript{−1} \textsuperscript{−1}</th>
<th>Heart rate, beats/min</th>
<th>Ventilation, l/min</th>
<th>MAP, mmHg</th>
<th>W\textsubscript{peak}, W</th>
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<td>76</td>
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**W\textsubscript{peak}, forced expiratory volume in 1 s; MAP, mean arterial pressure; W\textsubscript{peak}, peak work load; V\textsubscript{O\textsubscript{2}, oxygen consumption.**
between instantaneous loading (measurements made the initial 10–30 s of EL) and after breathing against the load for 3 min; however, there was a small but significant decline in stroke volume (SV; \( P < 0.03 \)) with prolonged loading and an increase in HR. There was a clear drift in many variables during the 40% but primarily the 70% work level when the initial CTL condition was compared with the final CTL condition at each workload, particularly for HR. Because the EL and ELH conditions occurred midway through each study, the CTL conditions were averaged for comparison to the EL and ELH. Because the changes observed with prolonged EL were qualitatively similar to the instantaneous EL condition, these data were also averaged for comparison to CTL and ELH.

**Cardiovascular changes with EL and ELH.** Changes in HR, CO, SV, and MAP with EL and ELH are shown in Fig. 1. EL resulted in a significant fall in CO at rest and during exercise (\( P < 0.05 \)) with the relative change (% change) diminishing with exercise. The fall in CO was due exclusively to a fall in SV because HR was either unchanged or higher than the corresponding CTL conditions. The SV was lower at the end of the EL period compared with the onset of EL, although CO remained constant due to a drift in HR. ELH resulted in a return of CO to levels not statistically different from the CTL condition. Again, this was due primarily to an increase in SV but also to a rise in HR. There was a small rise in MAP with EL at rest and at the 40% work level (\( P = 0.06 \)).

**Respiratory changes with EL and ELH.** Changes in various respiratory variables (breathing pattern, timing, degree of lung inflation, EI index, and \( P_{ETCO_2} \)) are shown in Table 2. Over the three conditions (rest, 40% \( W_{peak} \), and 70% \( W_{peak} \)), the changes in these variables were qualitatively similar. EL resulted in minimal changes in ventilation to a slight hyperventilation (↑ \( P_{ETCO_2} \), ↓ minute ventilation; \( P < 0.01 \) at 40 and 70% \( W_{peak} \)). At rest and the 70% workload, both \( f \) and \( T_I/T_{tot} \) decreased with EL (\( P = 0.025 \), but \( V_t \) remained unchanged compared with the CTL condition, indicating that the relative time in expiration increased with EL. \( IC \) decreased with EL under all conditions (\( P < 0.05 \) for 40 and 70% work levels), and the lung-inflation EI index increased by 25% at rest and by 7–19% during exercise, reflecting a mild hyperinflation with EL alone (\( P < 0.05 \)).

ELH had no consistent effect on minute ventilation or \( P_{ETCO_2} \) at the three levels of exercise, although \( f \) increased during ELH compared with EL alone in all three conditions (\( P < 0.05 \)). \( T_I/T_{tot} \) remained similar to or slightly below the EL condition, which was consistent with a prolonged \( T_e \). As expected, marked hyperinflation was achieved with an average fall in \( IC \) of 1.56 liters at rest and 0.95 and 0.89 liter at 40 and 70% \( W_{peak} \), respectively [with an EL lung volume (EILV) achieving ~90% of the VC] (\( P < 0.05 \)).

**Changes in respiratory muscle mechanics with EL and ELH.** Figure 2 shows a six-panel display of tidal Pe and Pg volume loops at rest, 40% \( W_{peak} \), and 70% \( W_{peak} \). Each tidal loop represents the mean response of all subjects for a given condition plotted according to the mean \( IC \). With EL, peak expiratory Pe and Pg increased as expected; however, peak inspiratory Pe and Pg also tended to increase. ELH resulted in a fall in peak expiratory Pe and Pg and a trend toward more negative swings in inspiratory Pe and Pg.

Figure 3 shows the mean Pe and Pg time integrals under the various conditions. Each point represents the mean integral for one breath, although data were obtained by averaging integrals across several breaths during each condition in each subject. Thus the change in the integral does not reflect changes in \( f \). Shown are the \( T_I \) and \( T_e \) integrals along with the mean time integral (accounting for changes in inspiratory and expiratory timing). The clear response is a large increase in expiratory Pg and Pe generation (\( P < 0.02 \)), suggesting recruitment of abdominal and rib cage accessory muscles with EL, with little change in inspiratory muscle recruitment. With hyperinflation, both the Pe and Pg \( T_e \) and mean time integrals fall, which is consistent with the fall in peak Pe and Pg observed in Fig. 2 and a reduction in expiratory muscle recruitment.

**Relationship of respiratory pressures to changes in cardiac function with EL and ELH.** We examined the relationship between the changes in respiratory pressures (end-expiratory and EI Pe and Pg as well as the changes in the pressure-time integrals) with EL and the change in pressures with ELH.
relative to the changes observed in cardiac function (SV and CO). Comparisons were made between CTL, EL, and ELH conditions. Although no striking relationships were observed, there was an association between the percent change in expiratory pressure and the percent change in cardiac function (change in expiratory Pe time integral and SV or CO, $R = -0.60, P < 0.01$; change in expiratory Pe time integral and SV, $R = -0.58, P < 0.01$; change in peak expiratory Pe and SV, $R = -0.57, P < 0.01$) with EL and between inspiratory pressure changes and cardiac function (change in EI Pe and CO, $R = -0.72, P < 0.01$; change in inspiratory Pe time integral and CO, $R = 0.52, P < 0.01$) with ELH. Thus, with EL, the increase in both expiratory Pe and Pg correlated with a fall in SV and CO, whereas the improvement in cardiac function with ELH correlated more strongly with changes in inspiratory Pe. Figure 4 shows the relationship of SV to the change in the expiratory Pg time integral with EL and the relationship of CO to the change in EI Pe with ELH.

**DISCUSSION**

We were interested in the influence of an EL and changes in lung inflation on CO in healthy adults at rest and during mild- to moderate-intensity exercise. We found that breathing against a constant 10-cmH$_2$O expiratory pressure resulted in an immediate drop (initial 10–30 s of loaded breathing) in CO of $\sim 1$ l/min at rest and during exercise (regardless of work intensity), due entirely to a drop in SV. With more prolonged breathing against an EL, SV fell further; however, CO remained essentially constant due to a small rise in HR (at rest and during exercise). ELH resulted in a rise in CO toward CTL values.

Respiratory-related influences on CO. The interactions of breathing with cardiac function are complex (16). The majority of studies examining heart and lung interactions have focused on animal models or in humans in an intensive care setting at rest and in the supine condition (6, 11, 13, 15, 28, 30). These studies have suggested that changes in lung volume, Pe, Pg, and respiratory rate all potentially influence cardiac hemodynamics. In addition, there are neurally mediated interactions (e.g., influence of lung volume on sympathetic and vagal tone) and respiratory influences on ventricular interdependence that may also modulate CO (16). During exercise, these heart and lung interactions are further amplified by VR increases, changes in EILV and EELV, marked increases in Pe and Pg swings, and changes in respiratory rate. In addition, exercise results in an augmented venous return from the locomotor muscle pumps and a rise in SBP, the latter of which could influence cardiac afterload (34). The predominant view in healthy subjects has been that CO is primarily preload sensitive, and thus it may be anticipated that pressure and lung-volume changes may exert their influence primarily via an influence on venous return in our subjects (16).

The expiratory loading in our study resulted in significant increases in expiratory Pe, a slightly more negative inspiratory Pe, a positive shift in Pg, and a rise in EELV and EELV at rest and during exercise. A positive shift in Pe will raise right atrial pressure and central venous pressure and subsequently reduce the gradient for venous return; however, such a pressure change will also reduce left ventricular transmural pressure and potentially reduce afterload (6, 28). Although the rise in Pe in the present study occurred only during expiration, the mean
shift (considering inspiration and expiration together) in Pe with expiratory loading was still positive (see Fig. 3). The expiratory loading also resulted in a mean positive shift in Pg. Elevations in Pg (secondary to abdominal muscle or diaphragmatic contraction) have been shown to decrease venous return from the legs in humans and, in turn, decrease the flow of blood through the inferior vena cava via a "starling resistor" mechanism (32). In our study, the highest correlation was observed between changes in CO or SV and changes in Pg with loading, suggesting that the positive Pg may play a significant role in inhibiting venous return and reducing CO.

The EL also resulted in a shift in the operational lung volume toward TLC (rise in EELV and EILV). Previous studies (26, 33) have suggested that, because the lungs and the heart share a common surface area, the higher lung volumes could reduce cardiac compliance and subsequently reduce cardiac filling and SV. Lung inflation has also been shown to mechanically compress the inferior and superior vena cava (reducing venous return) and result in a rise in pulmonary vascular resistance (16, 26, 33). However, we did not find a relationship between the changes in our index of lung inflation and the observed changes in SV or CO, suggesting that lung inflation had minimal influence on the fall in CO. Interestingly, even with further increases in EILV toward TLC by voluntary hyperinflation, no further reductions in SV or CO were noted, and in fact CO increased back toward preloading values. In a previous study (20), our laboratory markedly reduced VC in healthy subjects with chest wall restriction and greatly increased the competition for intrathoracic space between the heart and lungs. Although CO fell with chest wall restriction, it did not appear to be due to a lung volume-dependent mechanism. The healthy lung has been shown to have a very low shear modulus (especially at lower lung volumes), making it more likely to be deformed rather than compressing or deforming another object (such as the heart) (27). The fact that CO tended to return toward CTL values with voluntary hyperinflation and that these changes were most related to the more negative swings in inspiratory Pe changes suggests that CO is much more sensitive to changes in pressure than to lung volume.

Influence of expiratory-loading duration. At rest and during each exercise load, we assessed immediate changes in CO (first 30 s) with loading and changes after 2 min of loading. As a group, SV was further reduced with prolonged loading with a slight HR compensation, making CO constant during the EL. The mechanism for the further reduction in SV, although small, is unclear, because it would be expected that the majority of EL-related changes would occur immediately. We did find a small (nonsignificant) rise in MAP with the prolonged loading during exercise, which may have increased left ventricular afterload, contributing to the slight reduction in SV (16). The increase in MAP would be expected to have minimal impact on the gradient for venous return, since this would likely be a small influence relative to the pressures created by the contracting leg muscles.

Fig. 2. Esophageal (Pe; A) and gastric (Pg; B) pressure vs. volume loops at rest and during exercise. Each panel shows the average pressure-volume loop for all subjects during the 3 breathing conditions. Solid lines, C; dashed lines, EL; dash-dot lines, ELH.
Interaction of exercise intensity with expiratory loading. It did not appear that the influence of EL was enhanced or significantly reduced with higher exercise intensities. However, this depends on how our results are expressed. We found a similar absolute fall in CO across work levels but a relatively reduced fall in CO with higher work intensities when the fall is expressed as a percentage of the total CO. We found more positive Pg and Pe changes during expiration at the higher work intensities, and thus a greater percentage drop in CO may have been anticipated. It is possible that other factors, such as an augmented venous return from the muscle pumps, may have played a role in overcoming the influences of the EL. It is known that venous return from the muscle pumps is enhanced with more rapid muscle contractions; however, it is not clear what influence intensity of contraction may have had on venous return in our study (29). Previous studies have suggested that even light contractions may completely empty the venous circulation in the legs, and thus a more intense contraction may have little added benefit. We also did not keep track of pedaling frequency during the loading or during exercise intensity changes and thus cannot comment on the possible role of cycling cadence throughout the studies.

Previous studies in normal subjects. Prior work on EL and cardiac function has been complicated for a number of reasons. As noted previously, many studies examined patient populations in intensive-care settings under various levels of sedation and wakefulness (7–9, 11, 13, 30). There are also several studies in which EL is applied over only part of the expiratory phase or it is combined with loading or unloading of other parts of the breathing cycle (e.g., positive end-expiratory pressure breathing or continuous positive pressure breathing) (1, 4, 6, 12, 15). Few studies, however, have used small, physiological loads during expiration only, which may be more representative of the loads encountered in patients with obstructive lung disease.

Studies performed during exercise using continuous positive pressure breathing have found either no change in SV or CO with mild increases in pressure (4 cmH2O) to mild or moderate declines of 8 and 21% in CO with pressures of 15 and 30 cmH2O, respectively (1, 4). The influence of the EL alone during exercise, however, is unclear due to the added unloading of the inspiratory muscles in these studies and the likely influence of the reduced negative swing in inspiratory Pe on cardiac function.

Goldstein et al. (12) examined the influence of expiratory threshold loading (5–40 cmH2O) on breathing pattern and timing but on not cardiac function. They found that loading caused a mild hyperventilation in some subjects at rest and a progressive hypoventilation in most subjects during exercise. They also found a rise in PETCO2 with >10 cmH2O expiratory loads, small changes in VT, a drop in f and IC, and a rise in ELV. These changes were associated with consistent increases in Ti and Te during heavy and maximal exercise. These findings are consistent with the changes in breathing pattern observed in our study with EL; however, our subjects tended to demonstrate a prolongation of Te and thus a reduction in Ti/Ttot.

Fig. 4. A: relationship of the percent change in SV vs. the change in Exp Pg time integral going from the C to the EL condition. B: change in CO vs. the change in end InsP Pe going from the EL to the ELH condition.
Application to patients with lung disease. Patients with COPD have reduced exercise tolerance due both to an increased sensation of dyspnea and significant leg fatigue, with the latter symptom occurring even in patients with severe COPD who clearly reached the limits of their lung function (3, 10, 22, 24). The pattern of airflow limitation in most patients is predominantly expiratory, with nearly normal inspiratory resistances, which causes an intrinsic EL, particularly at the increased ventilations of exercise. Work by Montes de Oca et al. (21) suggested that compromised cardiac function may play a role in the reduced exercise capacity, as did work by Potter et al. (24). Stewart and Lewis (31) found CO to be <80% of the predicted value during exercise in patients with severe COPD. Although a number of these patients may be limited by pulmonary hypertension, hypoxemia, or other reasons, the enhanced EL, which occurs in these patients, may be expected to further limit increases in CO and reduce blood flow to the working muscles, thereby causing leg fatigue. It is difficult to test the influence of the EL in patients with COPD, because it is difficult to take away or significantly alter their intrinsic load to breathing. Oelberg et al. (23) examined cardiac changes while subjects breathed heliox and room air; however, significant improvements in CO were not noted on heliox. Although the degree of unloading was not assessed and some studies have not observed significant pressure reductions with heliox, this study would suggest that the EL may not be the key limiting factor in patients with severe COPD (1a).

Other studies have clearly supported a negative influence of lung mechanics and ELs on cardiac function. Hortop et al. (14) demonstrated a strong relationship between the changes in SV with exercise and the forced expiratory volume in 1 s in patients with cystic fibrosis. The altered SV in response to exercise was noted to be partly reversible with reduced expiratory-flow limitation during exercise.

Expiratory loading as a model for COPD. Patients with COPD are exposed to increased ELs as well as progressive hyperinflation (3, 24). Work by Potter et al. (24) on patients with COPD suggested that expiratory pleural pressures became positive even with mild exercise and were typically positive throughout expiration. The rise in expiratory pleural pressure occurs not only due to expiratory flow limitation at the lower lung volumes (intrinsic positive end-expiratory pressure) but also due to the significant recruitment of expiratory muscles early in expiration in an attempt to take advantage of the higher available flows at the higher lung volumes. A major difference between our model, which clamped expiratory pressures at 10 cmH2O throughout expiration and COPD, is that COPD tends to be a more lung volume-dependent load. In some cases, a patient will produce large expiratory pressures early in expiration to take advantage of the higher flow available at the higher lung volumes, whereas other subjects may attempt to breathe against narrowed or closed airways, resulting in higher expiratory pressures at the lower lung volumes (24). With increases in ventilatory demand, EELV rises until EILV approaches TLC. Thus, in disease, the load may be more variable and the extent of hyperinflation due to loading may be greater than under our simulated conditions. We attempted to accentuate the potential lung-volume influence by having subjects voluntarily breathe near TLC with an EL. This may have slightly amplified the negative swings in inspiratory pressures, although COPD patients would also need to create more negative pressures during inspiration to achieve adequate lung inflation.

In summary, our study suggests that a mild to moderate EL limits CO primarily through an influence on Pg and Pe, whereas changes in lung volume appear to minimally influence CO in healthy subjects.

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