Expiratory muscle fatigue does not regulate operating lung volumes during high-intensity exercise in healthy humans

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Taylor BJ, How SC, Romer LM. Expiratory muscle fatigue does not regulate operating lung volumes during high-intensity exercise in healthy humans. J Appl Physiol 114: 1569–1576, 2013. First published April 4, 2013; doi:10.1152/japplphysiol.00066.2013.—To determine whether expiratory muscle fatigue (EMF) is involved in regulating operating lung volumes during exercise, nine recreationally active subjects cycled at 90% of peak work rate to the limit of tolerance with prior induction of EMF (EMF-ex) and for a time equal to that achieved in EMF-ex without prior induction of EMF (ISO-ex). EMF was assessed by measuring changes in magnetically evoked gastric twitch pressure. Changes in end-expiratory and end-inspiratory lung volume (EELV and EILV) and the degree of expiratory flow limitation (EFL) were quantified using maximal expiratory flow-volume curves and inspiratory capacity maneuvers. Resistive breathing reduced gastric twitch pressure (−24 ± 14%, P = 0.004). During EMF-ex, EELV decreased from rest to the 3rd min of exercise [39 ± 8 vs. 27 ± 7% of forced vital capacity (FVC), P = 0.001] before increasing toward baseline (34 ± 8% of FVC end-exercise, P = 0.073 vs. rest). EILV increased from rest to the 3rd min of exercise (54 ± 8 vs. 84 ± 9% of FVC, P = 0.006) and remained elevated to end exercise (88 ± 9% of FVC). Neither EELV (P = 0.18) nor EILV (P = 0.26) were different at any time point during EMF-ex vs. ISO-ex. Four subjects became expiratory flow limited during the final minute of EMF-ex and ISO-ex; the degree of EFL was not different between trials (37 ± 18 vs. 35 ± 16% of tidal volume, P = 0.38). At end exercise in both trials, EELV was greater in subjects without vs. subjects with EFL. These findings suggest that 1) contractile fatigue of the expiratory muscles in healthy humans does not regulate operating lung volumes during high-intensity sustained cycle exercise; and 2) factors other than “frank” EFL cause the terminal increase in EELV.

Abdominal muscles; end-expiratory lung volume; expiratory flow limitation; ventilatory constraint

In healthy humans, active recruitment of the expiratory muscles during mild-to-moderate dynamic exercise serves to increase expiratory airflow and decrease end-expiratory lung volume (EELV) below functional residual capacity (FRC) (8, 10, 28). The decrease in EELV facilitates an increase in tidal volume (VT) and lowers the inspiratory work of breathing by placing the diaphragm in a better mechanical position to generate pressure (25). In addition, a decrease in EELV assists lung volume expansion at the initiation of inspiration by enhancing passive recoil of the chest wall (1). During high-intensity to maximal exercise, however, EELV has been shown to increase toward or even above FRC in healthy women (7, 38), highly fit elderly men (14), and endurance-trained athletes (15, 18, 21). An increase in EELV above resting preexercise values with a concomitant increase in end-inspiratory lung volume (EILV) (i.e., dynamic lung hyperinflation) increases the work and cost of breathing (15), heightens the perception of dyspnea (11, 15), may play a role in exercise-induced diaphragm fatigue (4, 12) and arterial hypoxemia (37), and ultimately contributes to impaired exercise tolerance (3, 11, 29).

While EELV is likely regulated by many factors that influence both the rate of lung emptying and inspiratory time, several studies have identified the development of substantial expiratory flow limitation (EFL) as a primary determinant of dynamic lung hyperinflation during exercise (3, 14, 18, 23, 24). For example, using an increase in barometric pressure to substantially decrease maximal expiratory flow, O’Kroy et al. (23) reported that the occurrence of EFL increased EELV during exercise, an effect that was likely due to dynamic compression of the airways downstream of the flow-limiting segment with a reflexively triggered premature termination of expiration (2, 3, 24).

Although the aforementioned evidence is suggestive that the increase in EELV commonly observed during high-intensity exercise is coincident with the occurrence of EFL, dynamic lung hyperinflation has also been shown to occur in the absence of EFL (21). Moreover, there is evidence that the occurrence of EFL during exercise is not always associated with an increase in EELV in normal healthy men (11), endurance-trained athletes (15), and patients with chronic cardiovascular disease (13), despite apparent room to increase EELV by encroachment on inspiratory reserve volume. Thus it appears that factors other than the presence of frank EFL contribute to the increase in EELV during exercise.

Recently, we (31) and others (36) have shown that expiratory muscle fatigue (EMF) occurs in response to high-intensity exercise sustained to the limit of tolerance. Prior induction of EMF has been associated with an increase in tidal expiratory pressure that may, in theory, augment dynamic airway compression, causing a reduction in expiratory time during subsequent exercise (32). Moreover, we (34) have demonstrated that EELV increases at the onset of exercise in individuals with significant expiratory muscle weakness secondary to cervical spinal cord injury, despite no evidence of EFL. Thus it is possible that fatigue and/or weakness of the expiratory muscles, together with the consequent perturbations in breathing pattern and respiratory pressures, might contribute to the increase in EELV with high-intensity exercise. While the effects of inspiratory muscle fatigue on breathing pattern has been studied (17, 30), the role of EMF in the regulation of operating lung volumes and breathing pattern during exercise is unknown. Accordingly, the primary aim of the present study was to determine whether EMF regulates EELV and breathing.
pattern during sustained high-intensity exercise in healthy humans. We, therefore, compared changes in operating lung volumes and breathing pattern during cycle exercise with and without prior induction of EMF. We reasoned that a greater increase in EELV with prior EMF would support the notion that EMF has an important role in the regulation of operating lung volumes during exercise.

MATERIALS AND METHODS

Subjects

Nine healthy, nonsmoking, recreationally active men participated in the study [mean ± SD age 28 ± 7 yr, stature 1.79 ± 0.07 m, body mass 82.8 ± 14.6 kg, peak work rate (Wpeak) 299 ± 55 W, peak O\textsubscript{2} uptake 51.0 ± 4.4 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}, peak O\textsubscript{2} uptake 126 ± 13% predicted]. The subjects had resting lung volumes and flow rates within normal limits (26) [forced vital capacity (FVC) 105% predicted]. The subjects abstained from food for 3 h, caffeine for 12 h, and exercise for 48 h before each session. During the first session, the subjects performed maximal incremental exercise (35 W every 3 min, starting at 95 W) on a stationary cycle ergometer (Excalibur, Lode, Groningen, the Netherlands) for the determination of W\textsubscript{peak} and associated parameters. Furthermore, the subjects were familiarized with magnetic nerve stimulation, expiratory resistive loading, and inspiratory capacity (IC) maneuvers. During the second session, the subjects performed cycle exercise to the limit of tolerance at 90% of W\textsubscript{peak} with prior induction of EMF (EMF-ex). EMF was induced by breathing against an expiratory flow resistor until task failure. During the final session, the subjects exercised for a time equal to that achieved in EMF-ex, but without prior induction of EMF (ISO-ex). Abdominal muscle contractility was assessed before and within 4 min after each exercise trial, as well as before and immediately after expiratory resistive loading during EMF-ex, by measuring the gastric twitch pressure (Pg\textsubscript{gas}) response to magnetic stimulation of the thoracic nerve roots. Changes in EELV and EILV and the degree of EFL during exercise were quantified using maximal expiratory flow-volume (MEFV) curves and IC maneuvers.

Magnetic Nerve Stimulation

Gastric pressure (P\textsubscript{ga}) and esophageal pressure (Pes) were measured using two latex balloon-tipped catheters (Ackrad Laboratories, Cooper Surgical, Berlin, Germany) passed pernasally into the stomach and lower one-third of the esophagus, respectively. The esophageal balloon was filled with 1 ml of air and was placed using the “occlusion” technique (5). The gastric balloon was filled with 2 ml of air to ensure that it did not collapse under high expiratory pressure (31). Each catheter was coupled to a differential pressure transducer (DP45; Validyne, Northridge, CA; range ±229 cmH\textsubscript{2}O) that was calibrated across the physiological range with an electro-manometer (model C9553, JMW, Harlow, UK). The pressure signals were amplified (CD280; Validyne), digitized at 150 Hz (micro 1401 mkl; Cambridge Electronic Design), and acquired and analyzed using commercially available software (Spike 2 version 7; Cambridge Electronic Design).

Subjects sat facing an inclined bench with hips flexed and chest supported. Magnetic stimuli were delivered to the thoracic nerve roots between the 8th (T\textsubscript{8}) and 11th (T\textsubscript{11}) thoracic vertebrae via a circular 90-mm coil powered by a magnetic stimulator (Magstim 200, Magstim, Whitley, UK). The area of stimulation that evoked the highest Pg\textsubscript{gas} was located, marked and used for all subsequent stimulations. Simulations were performed against a semiclosed airway at a relaxed end-expiratory Pes. To determine whether depolarization of the thoracic nerves in response to magnetic stimulation was supramaximal, three single twitches were obtained at 50, 60, 70, 80, 85, 90, 95, and 100% of the stimulator’s maximum power output. Each of the stimulations was separated by 30 s to avoid twitch potentiation. In agreement with our previous work (32), a clear plateau in Pg\textsubscript{gas} was not evident, despite a tendency for the group mean response to level off. That is, depolarization of the thoracic nerve roots in response to magnetic stimulation was likely submaximal.

Abdominal muscle contractility was assessed before (~20 min) and within 4 min of each of the exercise trials and the expiratory resistive loading protocol during EMF-ex. All stimulations were administered at 100% of the stimulator’s maximum power output, with each separated by 30 s. Four 1-Hz stimulations were delivered to the thoracic nerve roots such that four potentiated Pg\textsubscript{gas} values were obtained (baseline to peak). We also measured Pg\textsubscript{gas} ~5 s after a 5-s maximal expulsive maneuver performed against a semiclosed airway; this procedure was repeated six times such that six potentiated Pg\textsubscript{gas} values were obtained. The first two measurements were discarded because the degree of potentiation was slightly smaller after the first and, to a lesser extent, after the second expulsive effort.

Expiratory Resistive Loading

EMF was induced using a protocol that we have shown to elicit significant fatigue of the expiratory muscles, yet minimize fatigue of the diaphragm and inspiratory rib cage muscles (33). Briefly, subjects exhaled against a flow-resistive load provided by a variable aperture (MicroRMA, Micro Medical, Kent, UK), maintaining a respiratory frequency (f\textsubscript{r}) of 15 breaths/min and an expiratory duty cycle of 0.7, while targeting 40% of maximum expiratory P\textsubscript{ga}; inspiration was unimpeded. The target expiratory pressure was displayed on a computer screen, and subjects maintained f\textsubscript{r} and expiratory duty cycle by following a computer-generated audio signal. Subjects were instructed to maintain a constant P\textsubscript{ga} at the target level throughout each expiration. End-tidal partial pressure of CO\textsubscript{2} was not allowed to drop below eupneic values by manually adjusting the inspired fraction of CO\textsubscript{2}. Task failure was defined as an inability to generate the target pressure for three consecutive expiratory efforts, despite verbal encouragement.

Exercise Responses

Subjects cycled for 2 min at 40% of W\textsubscript{peak} before work rate was increased to 90% of W\textsubscript{peak}. Each subject pedaled at a self-selected cadence and maintained this cadence throughout. Volitional exhaustion was defined as the inability to maintain pedal cadence above 60 rpm. Ventilatory and pulmonary gas exchange indexes were measured using an ultrasonic flow meter (Birmingham Flowmeters, Birmingham, UK) and an online system (Oxycon Pro, Jaeger, Höchberg, Germany), respectively. Arterial oxygen saturation (Sp\textsubscript{O\textsubscript{2}}) and cardiac frequency (f\textsubscript{c}) were assessed via earlobe pulse oximetry (Ohmeda Biograph 3700e, BOC Healthcare, Louisville, CO) and telemetry (Polar Vantage NV, Polar Electro Oy, Kempele, Finland), respectively. Ratings of perceived exertion (dyspnea and leg discomfort) were obtained using Borg’s modified CR10 scale (6). P\textsubscript{ga} and Pes were measured throughout exercise and aligned to the airflow signal provided by the ultrasonic flow meter via predetermined delays. The
ventilatory and pulmonary gas exchange indexes [i.e., minute ventilation (Ve), fo2, Vt, O2 consumption, CO2 production, and derived variables], SpO2, fc, and peak Pga andPes during expiration were averaged for the 30 s before the first IC maneuver performed for that minute (see Operating Lung Volumes below).

Operating Lung Volumes

Operating lung volumes during exercise were quantified by measuring IC relative to FVC. IC maneuvers were performed in duplicate at rest, at the 1st min of exercise, every 2 min thereafter, and within 15 s before exercise cessation. Approximately 10–15 s before each IC maneuver, the subjects were given the prompt: “at the end of a normal breath out, take a maximal deep breath in.” This was followed by 5–10 further spontaneous breaths before the subjects were prompted to perform a second IC maneuver. Strong verbal encouragement to make a maximal inspiratory effort was given during each IC maneuver. To verify that a maximal inspiratory effort was made, we confirmed that peak inspiratory Pes during each IC maneuver matched that obtained at rest. If two acceptable measurements were obtained, IC was recorded as the mean value of the two maneuvers. EELV was calculated by subtracting IC from FVC, whereas EILV was calculated as the sum of Vt and EELV. Both EELV and EILV were expressed as a percentage of the FVC.

Expiratory Flow Limitation

Subjects performed three maximal volitional flow-volume maneuvers both before and within 2 min after exercise cessation during each trial. To account for exercise-induced bronchodilation, the MEVF curve was taken from the maneuver with the highest sum of FEVt and FVC, regardless of whether it was performed before or after exercise. Spontaneous tidal expiratory flow-volume curves (exEFV) were constructed from the 5–10 breaths preceding each IC maneuver and were plotted within the MEVF curve according to the measured IC. The degree of EFL was defined as the percentage of the exEFV curve that intersected the MEVF curve. Subjects were considered expiratory flow limited if >5% of the exEFV curve intersected the MEVF curve.

Statistical Analysis

Paired samples t-test was used to compare absolute measures of abdominal muscle contractility across time (pre- vs. postexercise) and the percent changes in these measurements between trials (EMF-ex vs. ISO-ex). Repeated-measures ANOVA was used to compare operating lung volumes and EFL across time (preexercise, 1st min of exercise, every 2 min thereafter, and end exercise). When significant main effects were detected, planned pairwise comparisons were made with the Bonferroni method. Paired samples t-test was used to compare the physiological responses to exercise, operating lung volumes, and the degree of EFL at equivalent time points between trials (EMF-ex vs. ISO-ex). The acceptable type I error was set at P < 0.05. Results are expressed as means ± SD. Statistical analysis was performed using SPSS version 12.0 for Windows (SPSS, Chicago, IL).

RESULTS

EMF

Task failure during expiratory resistive loading occurred at 25 ± 4 min. After the expiratory loading, there was a 9 ± 6% and a 24 ± 14% reduction in unpotentiated and potentiated Pgatw, respectively (P = 0.036 and P = 0.004). Immediately after exercise in EMF-ex and ISO-ex, Pgatw (unpotentiated and potentiated) was reduced below preexercise values (Fig. 1).

Exercise Responses

The subjects exercised for 7.18 ± 0.76 min during both EMF-ex and ISO-ex. The ventilatory, pulmonary gas exchange, and perceptual responses to EMF-ex and ISO-ex are shown in Table 1. Ve increased throughout exercise, reaching 96 ± 3% of peak values in EMF-ex. At the 5th and final minute of exercise, Ve was significantly greater in EMF-ex vs. ISO-ex. Most of the increase in Ve was accounted for by an increased contribution of ft consequent to a decrease in both inspiratory and expiratory time. Oxygen consumption and fc also rose steadily throughout exercise, reaching 99 ± 7% and 95 ± 3% of peak values in EMF-ex, and were not different compared with ISO-ex at any time point. SpO2 did not differ from baseline at any time point during either trial. Dyspnea and leg discomfort were rated higher at the 5th and final minute of exercise in EMF-ex vs. ISO-ex. Additionally, peak expiratory Pga and Pes were significantly elevated in EMF-ex vs. ISO-ex at the 5th and final minute of exercise.

Expiratory Flow Limitation

Figure 2 shows exEFV curves at rest, at the 3rd min of exercise, and at end exercise (ensemble average of 5–10 min after exercise). The percent decrease in Pgatw was greater after EMF-ex vs. ISO-ex for both unpotentiated (−18 ± 12 vs. −12 ± 10%, P = 0.031) and potentiated (−25 ± 14 vs. −12 ± 7%, P = 0.021) twitch measurements. That is, the severity of exercise-induced EMF was greater after EMF-ex vs. ISO-ex.
Table 1. Exercise responses for the 1st, 5th, and final minute of exercise

<table>
<thead>
<tr>
<th></th>
<th>EMF-ex</th>
<th>ISO-ex</th>
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<tr>
<td></td>
<td>1st min</td>
<td>5th min</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>51 ± 13</td>
<td>120 ± 19</td>
</tr>
<tr>
<td>fR, breaths/min</td>
<td>21 ± 6</td>
<td>38 ± 9</td>
</tr>
<tr>
<td>VT, liters</td>
<td>2.41 ± 0.46</td>
<td>3.26 ± 0.43</td>
</tr>
<tr>
<td>Ti, s</td>
<td>1.32 ± 0.25</td>
<td>0.82 ± 0.16</td>
</tr>
<tr>
<td>Te, s</td>
<td>1.56 ± 0.41</td>
<td>0.87 ± 0.21</td>
</tr>
<tr>
<td>Ti/TTOT</td>
<td>0.458 ± 0.017</td>
<td>0.485 ± 0.011</td>
</tr>
<tr>
<td>Te/TTOT</td>
<td>0.542 ± 0.011</td>
<td>0.515 ± 0.012</td>
</tr>
<tr>
<td>Vr/Ti, l/s</td>
<td>1.89 ± 0.47</td>
<td>4.09 ± 0.74</td>
</tr>
<tr>
<td>Vr/TTe, l/s</td>
<td>1.63 ± 0.46</td>
<td>3.95 ± 0.84</td>
</tr>
<tr>
<td>IC, liters</td>
<td>4.22 ± 0.76</td>
<td>4.20 ± 0.76</td>
</tr>
<tr>
<td>VCO₂, l/min</td>
<td>2.54 ± 0.40</td>
<td>3.90 ± 0.44</td>
</tr>
<tr>
<td>VCO₂, l/min</td>
<td>2.10 ± 0.51</td>
<td>4.41 ± 0.54</td>
</tr>
<tr>
<td>fC, breaths/min</td>
<td>137 ± 11</td>
<td>167 ± 14</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>97.2 ± 1.0</td>
<td>96.8 ± 0.8</td>
</tr>
<tr>
<td>RPE (dyspnea)</td>
<td>0.5 ± 0.8</td>
<td>8.4 ± 1.3</td>
</tr>
<tr>
<td>RPE (leg discomfort)</td>
<td>0.3 ± 0.7</td>
<td>8.7 ± 1.1</td>
</tr>
<tr>
<td>Peak expiratory Pgs, cmH₂O</td>
<td>15.8 ± 5.7</td>
<td>27.5 ± 9.4</td>
</tr>
<tr>
<td>Peak expiratory Pes, cmH₂O</td>
<td>−2.9 ± 2.4</td>
<td>13.1 ± 3.9</td>
</tr>
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</table>

Values are group means ± SD for 9 subjects. EMF-ex, exercise with prior induction of expiratory muscle fatigue; ISO-ex, exercise without prior induction of expiratory muscle fatigue; VE, minute ventilation; fR, respiratory frequency; VT, tidal volume; Ti, inspiratory time; Te, expiratory time; Ti/TTOT, fractional inspiratory time; Te/TTOT, fractional expiratory time; IC, inspiratory capacity; VCO₂, carbon dioxide output; VCO₂, oxygen uptake; VCO₂, respiratory frequency; SpO₂, arterial oxygen saturation; RPE, ratings of perceived exertion; Pgs, gastric pressure; Pes, esophageal pressure. *P < 0.05, †P < 0.01, values significantly different from EMF-ex at the same time point.

breaths) plotted within the MEFV curve during EMF-ex and ISO-ex in two representative subjects. One subject did not exhibit frank EFL at any time point during either exercise trial (Fig. 2, A and B), whereas the other became expiratory flow limited during both EMF-ex and ISO-ex (Fig. 2, C and D). During EMF-ex, frank EFL was present in two subjects at the 3rd min of exercise, in three subjects at the 5th min of exercise, and in four subjects (44% of study cohort) at end exercise (Table 2). At end exercise, 37 ± 18% (range 18–59%) of the exEFV curve encroached upon the boundary of the MEFV curve; this represented the maximum amount of EFL encountered by each subject. During ISO-ex, EFL was present in the same subjects and at the same time points compared with EMF-ex (Table 2). In addition, the severity of EFL at end exercise was not different in ISO-ex vs. EMF-ex (35 ± 16 vs. 37 ± 18%, P = 0.38). Thus prior induction of EFL did not influence either the occurrence or the severity of EFL during exercise.

Fig. 2. Ensemble average spontaneous tidal expiratory flow-volume curves generated from 5–10 breaths before the first inspiratory capacity maneuver at rest (R; thin solid line), at the 3rd min of exercise (3rd; dashed line), and at end exercise (End; dotted line) for EMF-ex (A and C) and ISO-ex (B and D) plotted within the maximal volitional expiratory flow-volume (MEFV) curve (thick solid line) based on the measured IC for two representative subjects. Note that the MEFV curve depicts the volume expired during the maximal maneuver only and does not account for residual volume. A and B: data for a subject who was not flow limited at any point during either EMF-ex or ISO-ex. C and D: data for an example subject who exhibited significant expiratory flow limitation (EFL) during the 3rd and final minute of exercise during EMF-ex and ISO-ex. Note that the degree of EFL in the subjects who exhibited this phenomenon was not different at any time point between EMF-ex and ISO-ex.
Figure 3. End-expiratory lung volume (EELV; A) and end-inspiratory lung volume (EILV; B) expressed relative to forced vital capacity (FVC) for EMF-ex (○) and ISO-ex (□). Values are group means ± SD for 9 subjects. **P < 0.01, values significantly different compared with baseline for both EMF-ex and ISO-ex. ††P < 0.01, EELV significantly increased from the 5th to the final minute of exercise for EMF-ex and ISO-ex.

Figure 4. EELV expressed relative to FVC for EMF-ex (A) and ISO-ex (B) in subjects who did not exhibit EFL (no EFL, ●) (n = 5) and in subjects who did exhibit EFL (EFL, ○) (n = 4). *P < 0.05, **P < 0.01; value significantly different in no EFL group vs. EFL group at the same time point. Note: EELV returned to resting values at end exercise during EMF-ex and ISO-ex in the no EFL group only.

Table 2. Expiratory flow-limitation during high-intensity exercise

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>V˙e flow limited, %</th>
<th>V˙e, l/min</th>
<th>V˙e flow limited, %</th>
<th>V˙e, l/min</th>
<th>V˙e flow limited, %</th>
<th>V˙e, l/min</th>
<th>V˙e flow limited, %</th>
<th>V˙e, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>62</td>
<td>41</td>
<td>104</td>
<td>42</td>
<td>123</td>
<td>34</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>68</td>
<td>0</td>
<td>97</td>
<td>29</td>
<td>119</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>86</td>
<td>10</td>
<td>110</td>
<td>18</td>
<td>131</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>96</td>
<td>55</td>
<td>109</td>
<td>59</td>
<td>154</td>
<td>50</td>
<td>92</td>
</tr>
</tbody>
</table>

Individual subject values for the percent of the spontaneous tidal expiratory flow-volume curve (ensemble average of 5–10 breaths) that met or exceeded the boundary of the maximal expiratory flow-volume curve during the 3rd min, the 5th min, and the final minute of exercise in EMF-ex and ISO-ex in the four subjects who exhibited expiratory flow-limitation are shown. The individual subject minute ventilation (V˙e) associated with that time point are also shown.

Operating Lung Volumes

Group mean changes in EELV and EILV from rest through to end exercise are shown in Fig. 3. During EMF-ex, EELV decreased from rest to the 3rd min of exercise (39 ± 8 vs. 27 ± 7% of FVC, P = 0.001) before increasing back toward resting baseline, such that EELV at end exercise was significantly greater vs. the 5th min of exercise, but not different compared with baseline (34 ± 8% of FVC at end exercise, P = 0.073 vs. rest). The maximum decrease in EELV occurred at the 1st min of exercise for one subject, at the 3rd min for six subjects, and at the 5th min for two subjects. EILV increased from rest to the 3rd min of exercise (54 ± 8 vs. 84 ± 9% of FVC, P = 0.006) and remained elevated to end exercise (88 ± 9% of FVC). Neither EELV nor EILV was different at any equivalent time point during EMF-ex vs. ISO-ex (P = 0.18 and 0.26, respectively). That is, the changes in operating lung volumes during exercise were not different with compared with without prior induction of EMF.

Figure 4 shows the differences in the EELV response to exercise during EMF-ex and ISO-ex between the subjects who did exhibit frank EFL (n = 4) and those who did not exhibit frank EFL (n = 5). Both groups decreased EELV from rest to the 3rd min of exercise in EMF-ex and ISO-ex. However,
while EELV at end exercise returned to resting levels in the no-EFL group during EMF-ex and ISO-ex, EELV remained lower relative to baseline values throughout exercise in EMF-ex and ISO-ex in the EFL group. Indeed, at both the 5th and final minute of exercise, EELV was significantly greater in the no-EFL group vs. the EFL group during EMF-ex and ISO-ex.

**DISCUSSION**

**Main Findings**

The main finding was that changes in operating lung volumes during sustained high-intensity cycle exercise were not different with compared with without prior induction of EMF. In addition, EFL occurred during exercise in only \( \sim 44 \% \) of the subjects. Neither the occurrence nor the severity of EFL was different following prior induction of EMF compared with during control exercise. Interestingly, EELV at end exercise was higher in the subjects who did not demonstrate frank EFL compared with those who did exhibit the phenomenon in both EMF-ex and ISO-ex. In combination, these findings suggest that 1) contractile fatigue of the expiratory muscles does not play a role in the regulation of operating lung volumes during high-intensity exercise in healthy humans; and 2) factors other than “frank” EFL cause the terminal increase in EELV.

**Technical Considerations**

*Supramaximal stimulation.* In agreement with our previous work (31), depolarization of the thoracic nerve roots in response to magnetic stimulation was likely submaximal in the present study. Despite this, all stimulations were performed at 100% of the stimulator’s maximum output, the coil position was marked in each subject before expiratory resistive loading and exercise to ensure that the coil was repositioned in exactly the same location for subsequent stimulations, and all stimulations were initiated at the same lung volume as judged by the same location for subsequent stimulations, and all stimulations were performed at 100% of the stimulator’s maximum output, the coil position was marked in each subject before expiratory resistive loading and exercise to ensure that the coil was repositioned in exactly the same location for subsequent stimulations, and all stimulations were initiated at the same lung volume as judged by the same location for subsequent stimulations, and all stimulations were initiated at the same lung volume as judged by the same location for subsequent stimulations. Although not measured in this study, we have shown previously that neither the amplitude nor the area of M waves evoked from the rectus abdominis is different before vs. after exercise (31). Thus we are confident that depolarization of the thoracic nerve roots via magnetic stimulation was kept constant throughout the study. The technical considerations associated with submaximal nerve stimulation have been discussed previously (16, 31, 35).

*Measurement of IC.* Our finding that operating lung volumes during high-intensity exercise is not regulated by EMF is critically dependent on the subjects’ ability to make a maximal inspiratory effort with each IC maneuver throughout exercise. A failure to correctly perform each IC maneuver, secondary to factors such as lack of subject effort, would cause an underestimation of IC with a consequent overestimation of EELV. In the present study, strong verbal encouragement to make a maximal inspiratory effort was given during each IC maneuver. Additionally, we discarded all IC maneuvers during which peak inspiratory Pes did not match that obtained at rest. Accordingly, group mean peak inspiratory Pes for the acceptable IC maneuvers was not different at rest vs. end exercise, or at any other time point, during EMF-ex and ISO-ex (−62 vs. −58 cmH\(_2\)O and −56 vs. −53 cmH\(_2\)O, respectively, \( P > 0.05 \)). Thus we are confident that poorly performed IC maneuvers did not contribute to our finding that prior induction of EMF does not alter the operating lung volume response to subsequent exercise.

**EMF: expiratory resistive loading vs. dynamic exercise.** One concern is that the demands placed on the expiratory muscles during expiratory resistive loading may not be representative of the normally occurring demands placed on these muscles during exercise. Any such discrepancy may lead to a subsequent over- or underestimation of the effect of the normally occurring level of EMF on operating lung volumes during exercise. In the present study, the degree of EMF induced by expiratory loading (\( \sim 24 \% \) reduction in potentiated P\(_{\text{ES}}\)) was remarkably similar to what we have previously reported following exhaustive whole body exercise (31, 32). We conclude, therefore, that the reduction in expiratory muscle function induced by expiratory loading was representative of the magnitude of EMF induced by the breathing requirements of high-intensity exercise.

*Intrathoracic gas compression.* An additional concern is that intrathoracic gas compression during the maximal expiratory maneuvers likely decreased the MEFV curves measured in each subject by an unknown amount. In theory, subsequent superimposition of spontaneously occurring expiratory flow volume curves during exercise within these “limited” MEFV curves may have caused us to overestimate or even falsely detect EFL. Indeed, in a recent study, Guenette et al. (9) reported that the severity of EFL during maximal exercise was significantly greater when assessed using MEFV curves obtained from expiratory maneuvers compared with MEFV curves constructed from expirations performed at different expiratory efforts (i.e., accounting for thoracic gas compression). However, EFL was overestimated by only \( \sim 5 \% \) when using postexercise MEFV curves that did not vs. those that did account for intrathoracic gas compression (9). In the present study, exercise-induced bronchodilation was taken into account by using the MEFV curve with the highest sum of F\(_{\text{E}}\)\(_{\text{V}}\) and FVC, regardless of whether it was performed before or after exercise. In addition, the least amount of EFL in any subject who exhibited it at end exercise was 16%. Thus, while we may have overestimated the severity of EFL, we are confident that EFL was not falsely detected in any of the subjects.

**Regulation of Operating Lung Volumes During High-intensity Exercise: No Role for EMF**

Active recruitment of the expiratory muscles of the rib cage and abdominal wall during mild- to moderate-intensity exercise augments expiratory airflow and decreases EELV below FRC (8, 10, 28). However, as exercise progresses toward high or maximal intensity, EELV has been shown to increase above FRC, such that dynamic lung hyperinflation occurs in fit healthy humans (14, 15, 18). Lung hyperinflation during exercise is associated with significant ventilatory constraint (18), an increase in inspiratory work (15), a heightened perception of breathlessness (11, 15), and exercise intolerance (3, 11, 29). While EELV is likely regulated by several factors that influence both the rate of lung emptying and expiratory time, the mechanism by which EELV rises during high-intensity exercise is still not fully understood. Previously, the development of substantial EFL has been identified as a primary trigger for
dynamic lung hyperinflation and the associated negative physiological sequelae (3, 14, 18, 23, 24). For example, Pellegrino et al. (24) demonstrated that application of an expiratory threshold load during exercise in subjects without EFL caused a reduction in expiratory flow with a concomitant increase in expiratory time and EELV that was abolished when the threshold load was removed. Similarly, with healthy subjects exercising at 3 ATM, where maximal expiratory flow is substantially decreased, O’Kroy et al. (23) reported that the occurrence of EFL had no effect on either VT or ventilation but increased EELV. In combination, these findings suggest that the development of EFL has a central role in the regulation of operating lung volumes, especially EELV, during high-intensity exercise. Although still somewhat speculative, it has been suggested that the increase in EELV with the occurrence of EFL is caused by a reflex inhibition of respiratory motor output and a subsequent premature termination of expiration secondary to compression of the airways downstream of the flow-limiting segment (2, 3, 24).

The findings detailed above provide compelling evidence that the increase in EELV commonly observed during high-intensity exercise is coincident with the occurrence of EFL. However, EELV has also been shown to increase during exercise in the absence of EFL. For example, Mota et al. (21) reported that, after an initial decrease, EELV gradually returned to resting values during high-intensity exercise, despite the presence of EFL in only one subject. Conversely, but in support of the notion, it has been shown in both healthy subjects (11, 15) and patients with heart failure (13) that the onset of EFL during exercise does not always induce an increase in EELV, despite apparent room to increase EELV by encroachment on the inspiratory reserve volume. Moreover, Dominelli et al. (7) observed that EELV was higher throughout progressive cycle exercise to exhaustion in young women without EFL compared with those with EFL. Together, the aforementioned observations suggest that factors other than the presence of “frank” EFL contribute to the terminal increase in EELV during high-intensity exercise.

Recently, we and others have shown that the expiratory muscles fatigue in response to high-intensity exercise sustained to the limit of tolerance in young, healthy recreationally active men (31, 32, 36). It is unlikely that de-recruitment of fatiguing expiratory muscles explains the increase in EELV, as both Ve and Pga continue to increase as EELV increases with increasing exercise intensity (10, 18, 31). However, it is conceivable that EMF may play a role in regulating operating lung volumes through two primary mechanisms. First, fatigue of the expiratory muscles may cause them to transiently weaken, facilitating an increase in EELV. We have previously found a sudden and sustained rise in operating lung volumes, despite limited evidence of EFL, in Paralympic athletes with substantial expiratory muscle weakness (34). Additionally, Mota et al. (22) reported that EELV measured during exercise at 70% of W_peak was inversely related to baseline expiratory muscle endurance in patients with obstructive pulmonary disease. Second, EMF may play a role in regulating operating lung volumes through a reduction in expiratory time. We have previously shown that prior induction of EMF is associated with a significant increase in expiratory Pes and Pga with a concomitant decrease in expiratory time during subsequent exercise (32). Theoretically, augmentation of expiratory intrathoracic pressure during exercise may increase the severity of dynamic airway compression and thus reflexively trigger a premature termination of expiration with a consequent reduction in expiratory time. It is also possible that the reduction in expiratory time is caused by modulation of respiratory motor drive secondary to activation of thin fiber group III and IV muscle afferents by metabolic alterations, coincident with fatigue of the expiratory muscles, as shown previously for the diaphragm (27). Regardless of its etiology, we theorized that a reduction in expiratory time associated with EMF, in combination with expiratory muscle weakness, would contribute to the increase in operating lung volumes, specifically EELV, commonly documented during high-intensity exercise. In the present study, EMF caused a significant reduction in expiratory time and a significant increase in both peak expiratory Pes and Pga (Table 1). Despite these changes, however, operating lung volumes during exercise were not different with compared with without prior induction of EMF. Thus it appears that contractile fatigue of the expiratory muscles does not play a significant role in the regulation of operating lung volumes during high-intensity exercise in healthy humans.

“Impending” Flow Limitation and Control of EELV During Exercise

An interesting, and at first glance paradoxical, finding of the present study was that a terminal increase in EELV occurred in subjects who did not exhibit EFL, whereas EELV remained significantly below resting values in subjects who became flow limited during exercise. However, this observation is in agreement with the recent finding that EELV is higher throughout exercise in young women without EFL compared with those with EFL (7). Thus it appears that some subjects “choose” to increase EELV during high-intensity exercise, avoiding EFL and maximizing expiratory flow rates. Moreover, these findings suggest that complete physical limitation of the airways is not needed to induce dynamic lung hyperinflation during exercise. Indeed, it has been shown that the onset of dynamic airway compression can start at expiratory flow rates ~2 l/s below maximal expiratory flow (19). That is, the onset of dynamic airway compression and the subsequent increase in airway resistance and changes in breathing pattern can start long before frank EFL is achieved. Thus, as previously proposed, it is highly likely that, when individuals approach their mechanical limit to generate expiratory flow, the airways begin to narrow or approach flow limitation, which reflexively triggers a premature cessation of expiration, initiates inspiration, and subsequently increases EELV (3, 18, 21, 24).

Conclusion

This study has shown for the first time that prior fatigue of the expiratory muscles in healthy individuals does not influence operating lung volumes during subsequent high-intensity constant-load cycle exercise. Moreover, it appears that increases in EELV during dynamic exercise cannot be readily explained by the occurrence or severity of EFL in healthy, young men. These results support the idea that contractile fatigue of the expiratory muscles does not regulate operating lung volumes during exercise, and that increases in EELV may be initiated by “impending” rather than frank EFL.
DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES