Role of expiratory flow limitation in determining lung volumes and ventilation during exercise

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McClaran, Steven R., Thomas J. Wetter, David F. PEGELOW, and JEROME A. DEMPSEY. Role of expiratory flow limitation in determining lung volumes and ventilation during exercise. J. Appl. Physiol. 86(4): 1357–1366, 1999.—We determined the role of expiratory flow limitation (EFL) on the ventilatory response to heavy exercise in six trained male cyclists (maximal O2 uptake = 65 ± 8 ml·kg\(^{-1}\)·min\(^{-1}\)) with normal lung function. Each subject completed four progressive cycle ergometer tests in random order: two trials while breathing N\(_2\)O\(_2\) (26% O\(_2\)-balance N\(_2\)), one with and one without added dead space, and two trials while breathing HeO\(_2\) (26% O\(_2\)-balance He), one with and one without added dead space. EFL was defined by the proximity of the tidal to the maximal flow-volume loop. With N\(_2\)O\(_2\) during heavy and maximal exercise, EFL was present in all six subjects during heavy (19 ± 2% of tidal volume (VT) intersected the maximal flow-volume loop) and maximal exercise (43 ± 8% of VT). 2) the slopes of the ventilation (ΔVT) and peak esophageal pressure responses to added dead space (e.g., ΔVe/ΔPET\(_{CO_2}\) where PET\(_{CO_2}\) is end-tidal PCO\(_2\)) were reduced relative to submaximal exercise, 3) end-expiratory lung volume (EELV) increased and end-inspiratory lung volume reached a plateau at 88–91% of total lung capacity, and 4) VT reached a plateau and then fell as work rate increased. With HeO\(_2\) (compared with N\(_2\)O\(_2\)) breathing during heavy and maximal exercise, 1) HeO\(_2\) increased maximal flow rates (from 20 to 38%) throughout the range of tidal volumes where EFL in all subjects during tidal breathing, 2) the gains of the ventilatory and inspiratory esophageal pressure responses to added dead space increased over those during room air breathing and were similar at all exercise intensities, 3) EELV was lower and end-inspiratory lung volume remained near 90% of total lung capacity, and 4) VT was increased relative to room air breathing. We conclude that EFL or even impending EFL during heavy and maximal exercise and with added dead space in fit subjects causes EELV to increase, reduces the VT, and constrains the increase in respiratory muscle output.
Table 1. Resting lung volumes and flow rates

<table>
<thead>
<tr>
<th>Lung volumes, liters</th>
<th>Measured</th>
<th>% Predicted</th>
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<tbody>
<tr>
<td>TLC</td>
<td>6.74 ± 0.44</td>
<td>105 ± 12</td>
</tr>
<tr>
<td>VC</td>
<td>5.20 ± 0.59</td>
<td>108 ± 18</td>
</tr>
<tr>
<td>RV</td>
<td>1.55 ± 0.39</td>
<td>99 ± 19</td>
</tr>
<tr>
<td>FRC</td>
<td>3.06 ± 0.36</td>
<td>100 ± 18</td>
</tr>
<tr>
<td>Flow rates</td>
<td></td>
<td></td>
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<tr>
<td>FEV 1, liters</td>
<td>4.28 ± 0.66</td>
<td>108 ± 18</td>
</tr>
<tr>
<td>FEV 1/FVC, %</td>
<td>84.1 ± 6.4</td>
<td>97 ± 20</td>
</tr>
<tr>
<td>Peak flow, l/s</td>
<td>9.80 ± 0.96</td>
<td>97 ± 22</td>
</tr>
<tr>
<td>MEF 50, l/s</td>
<td>6.17 ± 0.59</td>
<td>110 ± 25</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6. TLC, total lung capacity; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; FEV 1, forced expiratory volume in 1 s; FVC, forced vital capacity; peak flow, maximal expiratory flow; MEF 50, maximal expiratory flow after exhalation of 50% of VC. Predicted values are based on age and height (1).
and maximal exercise. Table 2 shows the response slopes of \( V\dot{E} \) and the nadir of inspiratory pressure to added dead space all expressed per Torr change in end-tidal PCO\(_2\) (PETCO\(_2\)). The slope of the ventilatory response to added dead space (\( \Delta V\dot{E}/\Delta\text{PETCO}_2 \)) was similar during the first four workloads of N\(_2\)O\(_2\) but was significantly reduced during heavy and maximal exercise (Table 2). During heavy and maximal exercise, \( V\dot{T} \) reached a peak and then fell at maximal exercise during N\(_2\)O\(_2\) breathing (Fig. 2B), with breathing frequency accounting for all the increases in \( V\dot{E} \). EELV was reduced at the onset of exercise, was maintained at these reduced levels during moderate-intensity submaximal exercise, and then rose during heavy and maximal exercise to approximate resting FRC (Fig. 3A). EILV showed a progressive increase during submaximal exercise, eventually reaching a plateau at 89–91% of TLC during heavy and maximal exercise (Fig. 3B).

Adding dead space increased \( V\dot{T} \) at all exercise intensities, accounting for most of the ventilatory response (Fig. 2B). Breathing frequency also increased with added dead space during mild and moderate exercise but then was unchanged or decreased slightly at heavy

![Figure 1: Relationship between minute ventilation (\( V\dot{E} \)) and end-tidal PCO\(_2\) (PETCO\(_2\)) during 6 incremental exercise workloads (52, 65, 74, 88, 95, and 100% of maximal O\(_2\) consumption (\( V\dot{O}_2\max \)), n = 6) when subjects were breathing N\(_2\)O\(_2\) (26% O\(_2\)-balance N\(_2\)) with no added dead space (ds), N\(_2\)O\(_2\) with 1 liter of dead space, HeO\(_2\) (26% O\(_2\)-balance He) with no added dead space, and HeO\(_2\) with 1 liter of dead space. Solid lines, ventilatory response to added dead space during N\(_2\)O\(_2\) breathing; dashed lines, ventilatory response to added dead space during HeO\(_2\) breathing. *Significantly different ventilatory response slope to added dead space from all 4 submaximal workloads with N\(_2\)O\(_2\) and all 6 workloads with HeO\(_2\) (see Table 2), \( P \leq 0.05 \). †Significantly different from N\(_2\)O\(_2\) breathing at same workload, \( P \leq 0.05 \).](http://jap.physiology.org/)

**Table 2.** Slope of ventilatory and Pes responses to added dead space

<table>
<thead>
<tr>
<th>( V\dot{O}_2\max %)</th>
<th>( \Delta V\dot{E}/\Delta\text{PETCO}_2 ), %l/Torr</th>
<th>( \Delta\text{Pes}/\Delta\text{PETCO}_2 ), cmH(_2)O/Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(_2)O(_2)</td>
<td>HeO(_2)</td>
</tr>
<tr>
<td></td>
<td>N(_2)O(_2)</td>
<td>HeO(_2)</td>
</tr>
<tr>
<td>52 ± 4</td>
<td>5.8 ± 4.2</td>
<td>5.3 ± 5.6</td>
</tr>
<tr>
<td>65 ± 5</td>
<td>7.1 ± 6.8</td>
<td>5.6 ± 6.6</td>
</tr>
<tr>
<td>74 ± 5</td>
<td>7.4 ± 8.2</td>
<td>4.2 ± 4.5</td>
</tr>
<tr>
<td>88 ± 5</td>
<td>6.3 ± 6.6</td>
<td>3.6 ± 2.3</td>
</tr>
<tr>
<td>95 ± 4</td>
<td>1.9 ± 2.0*</td>
<td>2.4 ± 1.2</td>
</tr>
<tr>
<td>100</td>
<td>1.1 ± 1.6*</td>
<td>3.1 ± 1.8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6. N\(_2\)O\(_2\), 26% O\(_2\)-balance N\(_2\); HeO\(_2\), 26% O\(_2\)-balance He; V\(\dot{E}\), minute ventilation; PETCO\(_2\), end-tidal PCO\(_2\); Pes, maximum inspiratory esophageal pressure. *Significantly different from other N\(_2\)O\(_2\) and all HeO\(_2\) workloads, \( P \leq 0.05 \). †Significantly different from other N\(_2\)O\(_2\) and all HeO\(_2\) workloads, \( P \leq 0.05 \).

![Figure 2: Relationship between breathing frequency (A) and tidal volume (VT, B) and \( V\dot{E} \) during incremental exercise (n = 6) when subjects were breathing N\(_2\)O\(_2\) (26% O\(_2\)-balance N\(_2\)) with no added dead space, N\(_2\)O\(_2\) with 1 liter of dead space, HeO\(_2\) (26% O\(_2\)-balance He) with no added dead space, and HeO\(_2\) with 1 liter of dead space. *Significantly different from N\(_2\)O\(_2\) with no added dead space, \( P \leq 0.05 \). †Significantly different from N\(_2\)O\(_2\) with 1 liter of dead space, \( P \leq 0.05 \).](http://jap.physiology.org/)
and maximal work intensities, respectively, accounting for the reduced ventilatory response to added dead space. The EILV increased slightly with added dead space at all work rates, accounting for most of the increase in VT. Small reductions in EELV also occurred with added dead space but only at light-intensity exercise (Fig. 3).

Expiratory flow limitation during exercise. Ensemble-averaged tidal flow-volume loops for rest and submaximal (74% of $V_{\text{O2max}}$), heavy (95% of $V_{\text{O2max}}$), and maximal exercise, along with the postexercise maximal voluntary flow-volume loop during $N_2O_2$ breathing with and without added dead space are shown in Fig. 4A. Expiratory flow limitation was nonexistent in all subjects without and with added dead space through the first three workloads. Without added dead space, all six subjects showed significant expiratory flow limitation during heavy (19 ± 2% of VT) and maximal exercise (43 ± 8% of VT), when $V_E$ exceeded 120 l/min. With the increased ventilatory response to added dead space, four subjects showed significant expiratory flow limitation during the fourth workload (12 ± 4% of VT) and all six subjects showed significant expiratory flow limitation during heavy (36 ± 9% of VT) and maximal exercise (45 ± 7% of VT).
Ensemble-averaged tidal pressure-volume loops for submaximal, heavy, and maximal exercise during N\textsubscript{2}O\textsubscript{2} breathing with and without added dead space are shown in Fig. 4B. As exercise intensity increased, there was a progressive decrease in nadir tidal inspiratory pressures and increase in peak tidal expiratory pressures. There was a significant response of inspiratory (nadir) and expiratory (peak) pressures to added dead space (ΔP\text{es}/ΔP\text{ETCO}_2) during submaximal exercise, and these response slopes were reduced during heavy and maximal exercise (Table 2, see Fig. 6).

Effect of the available maximal flow-volume envelope on expiratory flow limitation during exercise. We used HeO\textsubscript{2} to increase the size of the MFVL and, in turn, reduce the amount of expiratory flow limitation during exercise. The averaged MFVL with the ensemble rest and submaximal (74% of V\textsubscript{O2max}), heavy (95% of V\textsubscript{O2max}), and maximal exercise loops placed within the MFVL for the HeO\textsubscript{2} trials are shown in Fig. 5A. HeO\textsubscript{2} significantly increased maximal volitional expiratory flow rates at 75, 50, and 25% of VC by 2.7, 2.7, and 0.9 l/s, respectively, compared with N\textsubscript{2}O\textsubscript{2}. Throughout exercise, expiratory flow limitation was nonexistent in all subjects with no added dead space. With added dead space, there was some measurable, but minimal, expiratory flow limitation during HeO\textsubscript{2} breathing in three subjects (10 ± 14% of VT) only at maximal exercise. Thus HeO\textsubscript{2} eliminated or significantly reduced expiratory flow limitation during heavy and maximal exercise relative to N\textsubscript{2}O\textsubscript{2} (Fig. 4A).

Effect of reducing expiratory flow limitation via HeO\textsubscript{2} on ventilation, breathing pattern, and lung volume response to exercise and added dead space. The ventilatory response was unaltered with HeO\textsubscript{2} relative to N\textsubscript{2}O\textsubscript{2} breathing during the same submaximal exercise workloads up to 85% of V\textsubscript{O2max}. At heavy workloads with HeO\textsubscript{2} breathing, further hyperventilation occurred (i.e., increased Ve/CO\textsubscript{2} output ratio and decreased P\text{ETCO}_2) because of a higher VT and breathing frequency (Figs. 1 and 2). With HeO\textsubscript{2} breathing, the ventilatory response slope to added dead space (ΔVe/ΔP\text{ETCO}_2; Fig. 1, Table 2) was unchanged and similar to that with N\textsubscript{2}O\textsubscript{2} breathing over the first four workloads. At heavy and maximal exercise intensities, the mean ventilatory response to added dead space with HeO\textsubscript{2} breathing was reduced slightly but not significantly (P > 0.05) compared with lower workloads and was greater than the response slope during heavy and maximal exercise with N\textsubscript{2}O\textsubscript{2} breathing (Table 2, Fig. 1). The increased ΔVe/ΔP\text{ETCO}_2 response with added dead space during heavy and maximal exercise with HeO\textsubscript{2} vs. N\textsubscript{2}O\textsubscript{2} breathing was entirely due to an increased gain in breathing frequency (data not shown).

With HeO\textsubscript{2} breathing, VT rose linearly with increasing exercise intensity up to heavy exercise and then reached a plateau but did not fall during heavy and maximal exercise as Ve exceeded 130–140 l/min. These higher VT values during HeO\textsubscript{2} breathing (with no added dead space and with added dead space) in heavy and maximal exercise occurred because EELV remained reduced and below FRC rather than increased (as occurred during N\textsubscript{2}O\textsubscript{2} breathing), whereas EILV remained at ~90% of TLC and unchanged from that during N\textsubscript{2}O\textsubscript{2} breathing.

Ensemble-averaged tidal pressure-volume loops for submaximal, heavy, and maximal exercise and the
slope of the $\Delta P_{\text{Pes}}/\Delta P_{\text{PETCO}_2}$ during HeO2 with and without added dead space are shown in Fig. 5B. With increases in exercise intensity, added dead space caused a substantial decrease in peak inspiratory pressures. The slope of maximal inspiratory pressure to added dead space ($\Delta P_{\text{Pes}}/\Delta P_{\text{PETCO}_2}$) was not significantly different during submaximal, heavy, and maximal exercise with HeO2 (Table 2, Fig. 6). Thus, similar to the gain of the ventilatory response with HeO2 breathing, the slope of maximal inspiratory pressure to added dead space remained unchanged with increasing exercise intensity and during heavy and maximal exercise was significantly higher than with heavy and maximal exercise during N2O2 breathing (Table 2). Peak tidal expiratory Pes increased proportionately with increasing exercise intensity, although added dead space had little effect on expiratory Pes during HeO2 breathing at any workload (Fig. 5).

Ratings of dyspnea. During the N2O2 and HeO2 breathing with or without added dead space, dyspnea ratings increased slightly and progressively over the initial three workloads and then more steeply approached a maximal rating of 9–10 during heavy and maximal exercise intensities (Fig. 7). Added dead space caused increased dyspnea ratings at most workloads coincident with an increasing PETCO2, VE, and expiratory flow limitation, and this occurred with N2O2 and HeO2 breathing. Dyspnea ratings at a specific workload and with or without added dead space were not significantly influenced by HeO2 breathing, even though VE was higher and flow limitation was reduced during the HeO2 trials.

Fig. 6. Relationship between esophageal pressure (Pes) as percentage of capacity of inspiratory muscles to generate pressure ($P_{\text{cap,i}}$) and PETCO2 during 6 incremental exercise workloads (52, 65, 74, 88, 95, and 100% of VO2max, n = 6) when subjects were breathing N2O2 (26% O2-balance N2) with no added dead space, N2O2 with 1 liter of dead space, HeO2 (26% O2-balance He) with no added dead space, and HeO2 with 1 liter of dead space. Solid lines, Pes/Pcap,i response to added dead space during N2O2 breathing. Dashed lines, Pes/Pcap,i response to added dead space during HeO2 breathing. *Significantly different from all 4 submaximal workloads with N2O2 and all 6 workloads with HeO2 (see Table 2), P < 0.05.

Fig. 7. Perception of dyspnea during increasing exercise with and without added dead space and during N2O2 (air) and HeO2 (Heliox) breathing.

HeO2 breathing. Dyspnea ratings at a specific workload and with or without added dead space were not significantly influenced by HeO2 breathing, even though VE was higher and flow limitation was reduced during the HeO2 trials.

DISCUSSION

The purpose of this study was to determine whether mechanical constraints affected the ventilatory response and breathing pattern of heavy exercise. In the presence of significant expiratory flow limitation during heavy and maximal exercise, we observed an attenuated ventilation and reduction in the nadir of inspiratory Pes in response to added dead space relative to that obtained during submaximal exercise. With the removal of expiratory flow limitation via HeO2 breathing, the gain of the ventilatory response to added dead space was maintained throughout all exercise intensities. Further comparisons of N2O2 to HeO2 trials revealed that 1) when expiratory flow limitation was reduced with HeO2 (heavy and maximal exercise), VE was increased, but VE was not affected by HeO2 at submaximal workloads where no expiratory flow limitation was observed during the N2O2 trial; 2) HeO2 reduced expiratory flow limitation during heavy and maximal exercise and reduced EELV with no effect on EILV; thus the reduced EELV with HeO2 prevented the fall in VT during heavy and maximal exercise; and 3) HeO2 increased the gain of the reduction in peak inspiratory Pes with added dead space during heavy and maximal exercise. We believe that these correlative findings, together with the observed effects of the HeO2 breathing, demonstrate that the occurrence of expiratory flow limitation, even when less than one-half of the
VT is flow limited, is an important determinant of EELV, VT, and respiratory motor output and ventilation during heavy exercise.

Measurement of flow limitation. We used the proximity of the tidal breath to the maximal voluntary flow-volume loop (obtained immediately after exercise) to estimate the onset and degree of expiratory flow limitation incurred during exercise. During voluntary forced expiratory maneuvers, pleural pressures (Ppl) are sufficiently high so as to compress intrathoracic gas, and when flow rate and volume are measured at the airway opening (as we did), this “external” measurement of volume displacement will underestimate the true dimensions of the maximal expiratory flow-volume envelope (15). Accordingly, we may have overestimated the onset and/or magnitude of expiratory flow limitation during exercise. On the other hand, previous studies utilizing an independent measurement of the maximal effective transpulmonary pressure (Pmax) during expiration showed close agreement during heavy and maximal exercise between the degree of expiratory flow limitation as estimated from the tidal vs. maximal flow-volume envelope with that determined from the proximity of the tidal expiratory pressure to the Pmax (9, 17, 30). Furthermore, the expiratory Pes values we observed during heavy and maximal exercise were in excess of 20 cmH2O over a significant portion of expiration, and these values were previously shown to approximate Pmax in normal subjects (19, 30). We believe, then, that our measurements of the proximity of the tidal to the maximal voluntary flow-volume envelope are reasonably accurate estimates of significant expiratory flow limitation, especially during heavy and maximal exercise, where the tidal flow-volume envelope showed time and volume courses similar to the voluntary maximal flow-volume loop with which they were compared (9, 17, 34).

Nonetheless, our estimates did not identify true flow limitation in the classic sense, i.e., demonstrate a further change in transpulmonary pressure with no increase in expiratory flow rate (22). Indeed, as explained below (see Flow “limitation” and its compensatory responses are on a continuum), during heavy exercise there appeared to be many more instances where maximal expiratory flow and pressure were achieved over only a portion of the VT range at low lung volumes. We believe that these instances of “impending” complete flow limitation have substantial significance in the regulation of EELV and exercise hyperpnea.

Effects of expiratory flow limitation. Many studies have utilized an added chemical stimulus to examine the control of ventilation during exercise (4, 8, 17, 29, 33, 36). The significant ventilatory response we observed to added dead space during moderate exercise (Fig. 3) is consistent with previous studies that showed a vigorous ventilatory response to added inspired CO2 (8) and an increased VT with added dead space (29, 33, 36) in normal subjects throughout exercise. However, our observations of a significantly attenuated ventilatory response to added dead space during heavy exercise (vs. moderate-intensity exercise) agree only with those studies in which endurance-trained runners were used as subjects (4, 17). Johnson and co-workers (17) investigated the correspondence of significant expiratory flow limitation with the reduced ventilatory response to added chemical stimuli. They showed some increase in V̇E with added CO2, as long as there was room under the MFVL for increases in flow rate but a greatly attenuated or even no increase in V̇E in the presence of significant expiratory flow limitation. Although Clark and co-workers (4) did not measure expiratory flow limitation, they found that the attenuated ventilatory response to added inspired CO2 in endurance-trained men only occurred at a high ventilatory demand (>120 l/min), where in our experience some degree of expiratory flow limitation would likely occur in most subjects. We also note that some highly trained subjects have been reported to have exceptionally large MFVL and, therefore, may not experience expiratory flow limitation even at very high ventilatory requirements (2).

As workload increased, we showed a progressive parallel increase in breathing frequency and VT during submaximal exercise followed at higher workloads by a decreasing contribution of VT as breathing frequency accounted for most of the increases in V̇E during heavy exercise (Fig. 2). Notably, this decreasing relative contribution of VT to increases in V̇E began at a workload where no significant expiratory flow limitation was evident, suggesting that flow limitation was not mandatory. However, despite the lack of expiratory flow limitation when the decreasing contribution of VT began, EILV had risen above 85% of TLC (Fig. 3B). It would appear, therefore, that, to prevent lung volumes from encroaching on the stiffer portion of the lung and chest wall pressure-volume curves, increasing breathing frequency may have been the best available option for increasing V̇E. Furthermore, as our subjects progressed from heavy to maximal exercise, we observed a substantial rise in EELV (Fig. 3A), presumably caused by the onset of significant expiratory flow limitation. With an EILV at 90% of TLC, we also showed that VT actually decreased at maximal exercise relative to heavy exercise (Fig. 4B). Again, this suggests a mechanical constraint on VT in that further increases in EILV (>90% of TLC) do not appear to be an available option. The effects of increasing flow limitation on ventilation, breathing pattern, and lung volumes were also reflected in a reduced gain of the ventilatory response to added dead space.

The use of HeO2 provided us with an important tool to test experimentally the correlative evidence obtained during exercise with air breathing and with added dead space, as summarized above. We noted that HeO2 breathing was without significant effect on the ventilatory response to added dead space when expiratory flow limitation was not present. However, when flow limitation was eliminated by breathing HeO2 during heavy and maximal exercise intensities, hyperventilation ensued and the slopes of the ventilatory response to added dead space increased and approxi-
estimated the response gains observed during moderate exercise. Increases in EELV and reductions in Vt with heavy-intensity exercise and with added dead space were also prevented when expiratory flow limitation was eliminated via HeO2.

We interpret these correlations between expiratory flow limitation and reduced ventilatory response slopes, along with the observed effects of HeO2 breathing, to mean that when significant expiratory flow limitation is incurred during heavy exercise, EELV will increase, EILV will rise to within 10% of TLC, and increases in Vt and Ve will be constrained. What began then as a constraint on the ventilatory responses. Two types of evidence speak against this mechanism being a major contributor. First, unloading of inspiratory and expiratory muscle work (by as much as 50–60%) with use of a proportional-assist ventilator has shown little systematic effect on the ventilatory response to heavy or maximal exercise, even in highly trained subjects with V E > 150 l/min (10, 25). We do need to add the important caveat for these studies that a strong behavioral response to positive-pressure mechanical ventilation during exhaustive exercise may override any potential reflex feedback effects emanating from respiratory muscle unloading. Second, previous HeO2 breathing studies were conducted at high work rates in highly trained women (28). Although all these subjects produced comparably high levels of inspiratory flow rate and V E during exercise, not all experienced significant expiratory flow limitation. Among these women, the HeO2 influence on preventing the increase in EELV and enhancing Vt and Ve (as presently shown) occurred only in those who experienced measurable expiratory flow limitation during air breathing.

Flow “limitation” and its compensatory responses are on a continuum. The increase in EELV and the constrained response of Ve to added dead space began to occur when there was still substantial room within the maximal flow (and pressure)-volume envelope to increase expiratory and inspiratory flow rate and pressure. In fact, during submaximal heavy exercise intensities when the EELV began to increase and the ventilatory response to added dead space was significantly reduced, <40% of the Vt intersected the maximal flow-volume envelope. Furthermore, Ppl observed during tidal expiration approximated normal values for maximal, effective pressure during a brief fraction of expiration (17, 30). Also, on the inspiratory side, we estimated that peak Ppl would be only 60–70% of P gap,i (Fig. 6). As exercise intensity was increased to maximum, further increases in Ve caused more flow limitation, increased EELV, pushed inspiratory pressure closer to P gap,i, and caused greater reduction in and, in some cases, even flattened the slope of the Ve and Pes responses to added dead space. However, even under these circumstances, 20–30% of the maximal flow-volume envelope remained unused.

So, given that complete physical limitation of the airways to increased flow rate or of the inspiratory and expiratory muscles to increased force and pressure development is clearly not required to cause constraint of the ventilatory response during heavy exercise, we propose that some type of reflex inhibition of respiratory muscle output must occur in response to even minimal expiratory flow limitation during exercise.
Perhaps this proposed feedback effect is first triggered as the subject’s airways begin to narrow and “approach” flow limitation during expiration, which would reflexively terminate expiratory effort and initiate inspiration (3, 31). Then, as EELV rises, inspiratory motor output could be inhibited via lung stretch at high EELV. Limited evidence in lung transplant patients is consistent with some role for vagal feedback in regulating breathing pattern during heavy exercise in humans (34). Other indirect evidence in support of a disfacilitation or inhibition of respiratory motor output occurring during heavy exercise includes 1) the observation that tidal expiratory flow rates at the beginning of expiration do not instantaneously reach the boundary of the MFVL (19), 2) the substantial reduction in expiratory pressures produced during tidal breathing in maximal exercise compared with those produced by voluntary efforts in the resting subject for an identical flow-volume loop (14, 24), and 3) the finding that substantial amounts of hypoxia or hypercapnia superimposed on maximal exercise in fit subjects (17) (Fig. 1) caused no further increases in V̇ or flow rate or expiratory and inspiratory PES, suggesting that inspiratory and expiratory motor output were unresponsive to potent chemoreceptor stimulation under conditions of complete expiratory flow limitation.

Finally, it is certainly conceivable that high levels of several types of sensory input from chemoreceptors and from lung and chest wall mechanoreceptors may give rise to conscious perception of respiratory muscle force development and/or relative hyperinflation, which would also contribute importantly to modifications of respiratory motor output (20, 26). Although we observed increased dyspneic sensations in response to added dead space, these subjective ratings were not further influenced by superimposed HeO2 breathing. We cannot then correlate all observed changes in breathing pattern, EELV, and/or V̇ in response to alterations in flow limitation with changes in perception of breathing effort. However, given the wide variety of sensory inputs associated with exhaustive exercise and added chemical stimuli, it is perhaps not unexpected that subjects were unable to consciously discriminate all superimposed reductions in flow limitation.

Summary and relevance. The mechanical constraints to flow and volume have a significant influence on the ventilatory response, lung volumes, and breathing pattern during heavy exercise in those endurance-trained subjects who experience expiratory flow limitation. Two types of findings support this conclusion: 1) the reduction in the ventilatory response and increase in EELV with added dead space as tidal expiratory airflow intersected the MFVL in heavy exercise and 2) the prevention of these effects on EELV, V̇, and V̇̇̇̇ when HeO2 breathing was used to eliminate flow limitation. These data point to significant feedback inhibition of respiratory motor output during heavy exercise, which becomes evident under conditions of significant but not complete expiratory flow limitation. These mechanical constraints on V̇̇̇̇ likely explain, in part, why many highly trained subjects show relatively little hyperventilation during heavy exercise (7, 11, 12, 17). The result is that they fail to compensate for an excessively widened alveolar–arterial PO2 difference; thus arterial hypoxemia occurs and systemic O2 transport and VO2max are limited.

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