Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise

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Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. J. Appl. Physiol. 85(2): 609–618, 1998.—We have recently demonstrated that changes in the work of breathing during maximal exercise affect leg blood flow and leg vascular conductance (C. A. Harms, M. A. Babcock, S. R. McClaran, D. F. Pegelow, G. A. Nickele, W. B. Nelson, and J. A. Dempsey. J. Appl. Physiol. 82: 1573–1583, 1997). Our present study examined the effects of changes in the work of breathing on cardiac output (CO) during maximal exercise. Eight male cyclists [maximal O2 consumption (VO2max): 62 ± 5 ml·kg⁻¹·min⁻¹] performed repeated 2.5-min bouts of cycle exercise at VO2max. Inspiratory muscle work was either 1) at control levels [inspiratory esophageal pressure (Pes): −27.8 ± 0.6 cmH2O], 2) reduced via a proportional-assist ventilator (Pes: −16.3 ± 0.5 cmH2O), or 3) increased via resistive loads (Pes: −35.6 ± 0.8 cmH2O). O2 contents measured in arterial and mixed venous blood were used to calculate CO via the direct Fick method. Stroke volume, CO, and pulmonary O2 consumption (VO2pul) were not different (P > 0.05) between control and loaded trials at VO2max but were lower (−8, −9, and −7%, respectively) than control with inspiratory muscle unloading at VO2max. The arterial–mixed venous O2 difference was unchanged with unloading or loading. We combined these findings with our recent study to show that the respiratory muscle work normally expended during maximal exercise has two significant effects on the cardiovascular system: 1) up to 14–16% of the CO is directed to the respiratory muscles; and 2) local reflex vasconstriction significantly compromises blood flow to leg locomotor muscles.

There are several types of evidence that point to a significant role for the work of breathing (Wb) on the cardiovascular response to strenuous exercise. First, the Wb achieved at maximal O2 consumption (VO2max) in fit subjects was shown to require an O2 consumption (VO2) that equaled 10–15% of the VO2max, or 300–600 ml/min absolute VO2 (1). Presumably, this metabolic demand by the respiratory musculature would also require a significant share of the total cardiac output (CO). This presumption was confirmed by the high blood flows to respiratory muscles found during maximal exercise in animals (10, 11) but has not been tested directly in humans. Furthermore, 10- to 15-fold changes in intrathoracic pressure occur from rest to maximal exercise during inspiration and expiration; theoretically, these swings might be expected to influence the stroke output of the right and left heart (17, 19, 23, 24). Whether these changes in pressure actually cause a net change in stroke volume during exercise has also not been tested directly. Second, we recently found that vascular resistance in leg locomotor muscles during maximal exercise responded reflexly to imposed changes in the Wb, so that leg blood flow (Qlegs) increased with respiratory muscle unloading and decreased with respiratory muscle loading (8). We do not know how much, if any, of this change in local blood flow was attributable to coincident changes in CO; similarly, we do not know whether these changes in Qlegs induced by a changing Wb altered the proportion of total CO distributed to working locomotor muscles.

Our present study was aimed at determining the effects of changes in the Wb on CO during maximal exercise. We employed a proportional-assist ventilator (PAV) to unload, and fixed inspiratory resistances to the respiratory muscles during several bouts of maximal exercise in fit healthy subjects and used the direct Fick technique to measure any resultant changes in CO. We then combined these findings with our previous data on Qlegs under similar conditions (8) to quantify the partitioning of the CO normally achieved at VO2max to leg locomotor muscle and to respiratory muscles.

METHODS

Subjects. Eight male cyclists with resting pulmonary function within normal limits were recruited to participate in this study. Informed consent was obtained in writing from each subject, and all procedures were approved by the Institutional Review Board of the University of Wisconsin-Madison. The physical characteristics of the subjects were as follows: age, 29.5 ± 4.6 (SD) yr; height, 184.5 ± 3.1 cm; and weight, 71.1 ± 6.1 kg.

Pressure and gas measurements. During all tests, the raw data were recorded for subsequent analysis on an eight-channel Hewlett-Packard tape recorder, Gould chart recorder, and computer. Flow rates, flow-volume and esophageal pressure (Pes)-volume relationships, end-expiratory lung volume, and total body VO2 and CO2 production were measured by using equipment and techniques previously reported (1, 9). The Wb was defined as the integrated area of the pressure-volume loop (16). Wb multiplied by the breathing frequency represents the amount of work done per minute on the lungs. We note that our use of the area of the Pes-volume loop underestimates the actual Wb by variable amounts (1, 7); thus our measurements report only a conservative estimate of the total amount of work done by the

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respiratory muscles during exercise and their changes with unloading and loading.

Inspiratory unloading and loading. A feedback-controlled PAV was used to reduce the work of the inspiratory muscles during exercise (29). Briefly, subjects breathed through a Hans Rudolph valve that was connected (on the inspiratory side) to the PAV. The PAV contains a linear motor that drives a piston (filter volume capacity) which develops pressure in proportion to inspiratory airflow and volume. The level of assist is controlled by potentiometers on the control panel of the ventilator, and there are separate controls for volume assist and flow assist. During inspiration, the PAV makes mouth pressure positive in proportion to flow such that the proportional assist (unloading) of the respiratory muscles occurs throughout the inspiratory cycle. In practice, the amount of assist is set at the maximal level that each subject can tolerate, as determined from practice sessions before testing. During practice and testing sessions, subjects were verbally coached to relax and permit the PAV to assist each inspiration as much as possible.

To increase inspiratory work during exercise, we added ventilatory loads that consisted of mesh screens in the inspiratory line with resistances of 3–7 cmH2O·L−1·s−1. These resistances were sufficient at the high flow rates achieved in maximal exercise to increase the Wb by 20–80% above control levels. Subjects participated in practice sessions to familiarize themselves with the inspiratory loads.

CO and blood-gas measurements. A Swann-Ganz catheter was inserted under sterile conditions in the left brachial vein and advanced caudally to the pulmonary artery for sampling of mixed venous blood. The position of the catheter tip was verified via fluoroscopy. A 20-gauge arterial catheter (Arrow) was inserted percutaneously in the right brachial artery under local 1% lidocaine anesthesia. CO was calculated via the direct Fick method: CO = VO2arterial-mixed venous O2 difference (a-wDO2). The a-wDO2 was divided by arterial O2 content to give O2 extraction. Vascular resistance was calculated as the ratio of mean arterial blood pressure to CO.

Duplicate 3- to 10-ml samples of arterial and mixed venous blood were drawn anaerobically over 10–20 s during each test for measurement of PO2, PCO2, and pH with a blood-gas analyzer calibrated with tonometered blood (Radiometer ABL300), and for measurement of O2 saturation and hemoglobin with a CO-oximeter (Radiometer OSM 3). Blood gases were corrected for temperature changes during exercise as measured from a thermocouple placed intranasally in the lower one-third of the esophagus lumen (Mon-a-Therm 6500) for arterial blood temperature and from a thermocouple located in the Swann-Ganz catheter for mixed venous blood temperature. Brachial artery and pulmonary arterial blood pressures (Ppa) were measured with Ohmeda pressure transducers (model P10E2) attached to the arterial and mixed venous line. Blood lactate concentration was analyzed by means of a lactate analyzer (model 1500 Sport; Yellow Springs Instruments). Hematocrit was determined by microcentrifuge.

Experimental protocols. Subjects initially completed a progressive incremental VO2max exercise test on an electromagnetically braked cycle ergometer (Elema) beginning at 150 W (30–40% VO2max) followed by an increase in work rate of 50 W every 2.5 min until exhaustion. Subjects selected their preferred pedaling frequency during the test, and this cadence was maintained constant throughout all subsequent testing through visual inspection of a digital cadence output. After a 20-min recovery, subjects cycled to exhaustion at 5–10% above their peak workload (WL) (as determined by the previous progressive test) to verify VO2max. A plateau (<150 ml) or decrease in VO2 was observed for each subject between the final two WL of the incremental VO2max test and/or between the final WL of the incremental test and the WL of the repeat test. The mean VO2max was 62 ± 5 ml·kg−1·min−1 (range 55–74 ml·kg−1·min−1).

On a separate day, and after placement of the catheters, subjects completed several exercise trials (separated by 15–20 min). Three trials were performed at a WL that was at the subjects’ VO2max WL (383 ± 33 W) and that could be maintained for 2.5–3.0 min (as determined from a separate practice session). These tests consisted of one trial with no ventilatory intervention (control), one trial of inspiratory muscle unloading, and one trial of inspiratory muscle loading. The first maximal trial of each day was a control trial, and the order of the remaining two trials was randomized. Control submaximal exercise bouts set at 50 and 75% of VO2max WL were also performed to establish a relationship between CO and VO2. During all exercise bouts, subjects first increased work rate progressively to the required WL over 30 s, and then three simultaneous collections of VO2 and blood sampling were taken at 45 s ± 1 min, 1 min 30 s ± 1 min 45 s, and 2 min 15 s ± 2 min 30 s.

Statistical analysis. Relationships between Wb and the dependent variables under the three conditions, control, inspiratory muscle load, and inspiratory muscle unload at VO2max WL, were determined from simple regression. ANOVA was used to determine treatment differences between group mean values under each of the three conditions. Tukey’s post hoc analysis was used to determine where the differences between pairs of mean values were present. Significance was set at P ≤ 0.05.

RESULTS

We present our findings concerning the effects of changing the Wb on several variables of O2 transport by showing 1) absolute values for each subject and 2) values as a percentage of control across all subjects. The group mean changes for each variable measured during inspiratory unloading, control, and inspiratory loading obtained during the final 2.5-min measurement period at VO2max are summarized in Tables 1 and 2.

Table 1 shows the average change in Wb, peak inspiratory and expiratory Pes, and ventilatory output achieved with inspiratory unloading and loading. Inspiratory muscle unloading during maximal exercise reduced Wb by variable amounts to average 54.9 ± 6.2% of control, whereas with resistive loads Wb was increased to 156.7 ± 8.6% of control. Peak inspiratory Pes was increased 41 ± 3% with inspiratory unload (less negative) and was reduced 22 ± 4% with inspiratory loading (more negative). Peak expiratory Pes was reduced by 24 ± 3% with inspiratory unload (less positive) but was not different from control with inspiratory loading. The difference between peak inspiratory and peak expiratory Pes was 50 cmH2O during control, 34 cmH2O during unloaded trials, and 59 cmH2O during loaded trials. Tidal volume, breathing frequency, minute ventilation (Ve), arterial and mixed venous PCO2, pH, PO2, O2 saturation, lactate, and hemoglobin did not change systematically (P > 0.05) across the range of Wb values within each subject (see Table 1). The ratio of inspiratory time to total time was 0.48 ± 0.09 during unloading, 0.49 ± 0.12 during control, and 0.56 ± 0.13 during loading.

Effects of changing Wb on O2 transport. Figure 1A shows individual absolute values for VO2, CO, and...
Table 1. Effect of increasing and decreasing the Wb at V\textsubscript{O2max} workload on ventilation and blood gases

<table>
<thead>
<tr>
<th>Wb (%control V\textsubscript{O2max})</th>
<th>Inspiratory Unload</th>
<th>Control</th>
<th>Inspiratory Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wb, J/min</td>
<td>54.9 ± 6.2</td>
<td>100</td>
<td>156.7 ± 8.6</td>
</tr>
<tr>
<td>Peak inspir. Pes, cmH\textsubscript{2}O</td>
<td>301.0 ± 21.6*</td>
<td>547.6 ± 36.3</td>
<td>858.1 ± 23.7*</td>
</tr>
<tr>
<td>Peak expir. Pes, cmH\textsubscript{2}O</td>
<td>-16.3 ± 0.5*</td>
<td>-27.8 ± 0.6</td>
<td>-35.6 ± 0.8*</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>162.9 ± 9.8</td>
<td>159.0 ± 11.2</td>
<td>149.0 ± 10.6</td>
</tr>
<tr>
<td>Ve, breaths/min</td>
<td>43.8 ± 2.5</td>
<td>46.3 ± 3.7</td>
<td>45.1 ± 3.6</td>
</tr>
<tr>
<td>Vt, liters</td>
<td>3.74 ± 0.14</td>
<td>3.50 ± 0.22</td>
<td>3.38 ± 0.23</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2}, Torr</td>
<td>91.7 ± 36</td>
<td>92.0 ± 2.6</td>
<td>88.7 ± 2.4</td>
</tr>
<tr>
<td>P\textsubscript{a}O\textsubscript{2}, Torr</td>
<td>155.5 ± 21</td>
<td>163.3 ± 2.2</td>
<td>164.2 ± 2.2</td>
</tr>
<tr>
<td>S\textsubscript{aO\textsubscript{2}}%,</td>
<td>94.7 ± 0.5</td>
<td>95.2 ± 0.3</td>
<td>94.5 ± 0.3</td>
</tr>
<tr>
<td>S\textsubscript{vO\textsubscript{2}}%,</td>
<td>13.8 ± 15</td>
<td>15.8 ± 1.5</td>
<td>14.8 ± 1.5</td>
</tr>
<tr>
<td>P\textsubscript{a}O\textsubscript{2}, Torr</td>
<td>34.1 ± 20</td>
<td>33.1 ± 0.7</td>
<td>33.5 ± 1.2</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2}, Torr</td>
<td>71.4 ± 3.3</td>
<td>78.8 ± 2.3</td>
<td>75.2 ± 2.2</td>
</tr>
<tr>
<td>pH\textsubscript{a}</td>
<td>7.29 ± 0.03</td>
<td>7.33 ± 0.01</td>
<td>7.30 ± 0.02</td>
</tr>
<tr>
<td>pH\textsubscript{e}</td>
<td>7.14 ± 0.04</td>
<td>7.14 ± 0.04</td>
<td>7.13 ± 0.02</td>
</tr>
<tr>
<td>[L\textsubscript{a}a, mM]</td>
<td>9.21 ± 2.5</td>
<td>8.64 ± 1.40</td>
<td>9.58 ± 1.75</td>
</tr>
<tr>
<td>[L\textsubscript{a}h, mM]</td>
<td>9.48 ± 2.13</td>
<td>8.98 ± 1.36</td>
<td>9.90 ± 1.59</td>
</tr>
<tr>
<td>[Hb], g/dl</td>
<td>15.0 ± 0.2</td>
<td>15.0 ± 0.2</td>
<td>15.0 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. All values obtained during final 30 s of a 2.5-min exercise load. V\textsubscript{O2max}, maximal O\textsubscript{2} consumption; Wb, work of breathing: inspir. and expir., inspiratory and expiratory, respectively; Pes, esophageal pressure; Ve, minute ventilation; f, breathing frequency; Vt, tidal volume; a and v, arterial and mixed venous, respectively, values shown for PO\textsubscript{2}, O\textsubscript{2} saturation (SO\textsubscript{2}), PCO\textsubscript{2}, pH, and lactate concentration ([L\textsubscript{a}a]). *Significantly different from control (P < 0.05).

Table 2. Effect of increasing and decreasing the Wb at V\textsubscript{O2max} workload on O\textsubscript{2} transport, O\textsubscript{2} uptake, and vascular resistance

<table>
<thead>
<tr>
<th>Wb (%control V\textsubscript{O2max})</th>
<th>Inspiratory Unload</th>
<th>Control</th>
<th>Inspiratory Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wb, Cardiac output, l/min</td>
<td>24.1 ± 0.7*</td>
<td>26.5 ± 0.8</td>
<td>26.4 ± 0.8</td>
</tr>
<tr>
<td>a -v\textsubscript{DO2}, m/dl</td>
<td>16.9 ± 0.3</td>
<td>16.6 ± 0.3</td>
<td>16.7 ± 0.3</td>
</tr>
<tr>
<td>V\textsubscript{O2}, l/min</td>
<td>4.11 ± 0.16*</td>
<td>4.40 ± 0.15</td>
<td>4.40 ± 0.15</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>138.0 ± 5.3</td>
<td>149.3 ± 6.0</td>
<td>149.8 ± 5.1</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>175.1 ± 3.9</td>
<td>178.3 ± 4.6</td>
<td>176.3 ± 3.3</td>
</tr>
<tr>
<td>CaO\textsubscript{2}, ml/dl</td>
<td>20.0 ± 0.3</td>
<td>20.0 ± 0.3</td>
<td>19.9 ± 0.3</td>
</tr>
<tr>
<td>C\textsubscript{VO2}, ml/dl</td>
<td>2.9 ± 0.3</td>
<td>3.4 ± 0.4</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>O\textsubscript{2} extraction,</td>
<td>84.5 ± 0.3</td>
<td>83.0 ± 0.3</td>
<td>83.9 ± 0.3</td>
</tr>
<tr>
<td>Pulmonary arterial pressure, mmHg</td>
<td>32.5 ± 3.5</td>
<td>29.5 ± 2.7</td>
<td>25.5 ± 3.8</td>
</tr>
<tr>
<td>Pulmonary vascular resistance,</td>
<td>1.34 ± 0.13*</td>
<td>1.12 ± 0.10</td>
<td>0.97 ± 0.14</td>
</tr>
<tr>
<td>mean arterial pressure, mmHg</td>
<td>118.8 ± 7.8</td>
<td>125.2 ± 6.7</td>
<td>121.5 ± 8.1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>197.9 ± 7.2</td>
<td>210.4 ± 6.9</td>
<td>204.5 ± 7.8</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>79.3 ± 2.1</td>
<td>82.6 ± 2.4</td>
<td>80.9 ± 2.4</td>
</tr>
<tr>
<td>Total peripheral resistance, mmHg</td>
<td>4.96 ± 0.37</td>
<td>4.78 ± 0.31</td>
<td>4.64 ± 0.35</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. All values obtained during final 30 s of a 2.5-min exercise load. a-v\textsubscript{DO2}, arterial-mixed venous O\textsubscript{2} difference; V\textsubscript{O2}, O\textsubscript{2} consumption; CaO\textsubscript{2}, arterial O\textsubscript{2} content; C\textsubscript{VO\textsubscript{2}}, mixed venous O\textsubscript{2} content; BP, blood pressure. *Significantly different from control (P < 0.05).
reduction in CO amounted to 46% of the total reduction in CO actually observed with respiratory muscle unloading at \( \dot{V}\text{O}_2\text{max} \).

Next, to examine the effects of factors independent of \( \dot{V}\text{O}_2 \) that might have caused the reduction in CO with unloading, we compared two WLs of 1) near-equal \( \dot{V}\text{O}_2 \) (maximal work rate with unloading vs. 93% of \( \dot{V}\text{O}_2\text{max} \) control), but 2) with average intrathoracic pressures, which were different by 9 ± 1 and 7 ± 1 cmH₂O at peak inspiration and expiration, respectively (see Fig. 5A).
Note in Fig. 5A that stroke volume was higher in all subjects by 7 ± 1 ml (P < 0.05) when intrathoracic pressure was less negative (by 9 ± 1 cmH₂O), i.e., at 93% of V⁰₂max (P < 0.001), even though V⁰₂ was the same. Because heart rate fell an average of 5 ± 1 beats/min (P < 0.05) at the lower work rate, CO was not affected by the increased stroke volume. Note also that this increase in stroke volume between these two WLs was slightly less than one-half of the reduction in stroke volume achieved when respiratory muscles were unloaded at V⁰₂max.

Figure 5B shows the association of a changing negativity of Pes with respiratory muscle loading at V⁰₂max. Despite an almost 8 cmH₂O more negative peak inspiratory Pes with loading at V⁰₂max, stroke volume and CO remained unchanged.

**DISCUSSION**

Summary of findings. Our findings demonstrate a significant effect of respiratory muscle unloading on stroke volume and CO during maximal exercise in the healthy, trained human. We found that reducing the Wb via proportional-assist ventilation during maximal exercise caused significant decreases in V⁰₂ and in CO, due primarily to reduced stroke volume, whereas increasing the Wb during maximal exercise had no effect on CO or V⁰₂. Correlational analysis implied that the effect of respiratory muscle unloading on CO was attributable to reductions in metabolic demand (i.e., V⁰₂) by the respiratory muscles and/or to the effects of an increased (i.e., less negative) intrathoracic pressure.
on venous return. These findings, in combination with those we recently reported (8), demonstrate that the respiratory muscle work experienced under normal physiological conditions at maximal exercise exerts two types of effects on the cardiovascular response: 1) a substantial portion of the CO (up to 14–16%) is directed to the respiratory muscles to support their metabolic requirements; and 2) blood flow is reduced to (or “stolen from”) working locomotor muscles because of sympathetically mediated vasoconstriction induced reflexly and possibly originating in contracting respiratory musculature.

Speculation as to the cause of the unloading effect on CO. Why did CO decrease with respiratory muscle unloading at VO\(_2\)max? First, and most straightforward, the decreased respiratory muscle work and VO\(_2\) mean less demand for blood flow, and the reduced CO may merely have followed the well-established relationship of CO to whole body VO\(_2\) as determined over a wide range of increasing exercise intensities and with a variety of exercise modalities that involved predominantly the arms or leg cycling (see Fig. 4; Ref. 21). We used this regression equation obtained under control conditions to estimate that, when respiratory muscles were unloaded at VO\(_2\)max, about one-half of the reduction in CO was associated with (and predictable from) the reduction in VO\(_2\). This apparent dependency of reductions in blood flow on reductions in VO\(_2\) is consistent with the findings of Coast et al. (5) and Anholm et al. (3), who increased the Wb by using resistive loading or hyperpnea in subjects at rest and reported significant increases in heart rate, CO, and VO\(_2\). Because these increases in CO developed slowly (i.e., they required >20 s of hyperpnea), they were attributed to the associated changes in VO\(_2\). Therefore, we think it reasonable to suggest that at least a significant portion of the reduction in CO with respiratory muscle unloading during maximal exercise was attributable to a corresponding reduction in VO\(_2\).

However, it is important to note that the VO\(_2\)-CO relationship established across increasing work rates is dependent primarily on changes in heart rate (see Fig. 5; Ref. 20). This dependency of changes in CO on heart rate contrasts with the reduction in CO with respiratory muscle unloading that we observed during maximal exercise, which was primarily dependent on the reduction in stroke volume (see Fig. 1B). Furthermore, we also compared stroke volumes between conditions of equal VO\(_2\), i.e., the unloaded condition at maximal exercise vs. the control condition at an average of 93% of VO\(_2\)max (see Fig. 5), and observed that stroke volume was reduced during the unloaded condition. Therefore, these significant effects on stroke volume from respiratory muscle unloading (even at comparable VO\(_2\)) implied that some factor associated with the unloading, other than the reduced VO\(_2\), may also be important in determining CO. Perhaps increases in (i.e., less negative) intrathoracic pressures may have caused the reduced stroke volume.

Changes in intrathoracic pressure imposed primarily at rest in supine humans (18) and anesthetized animals (24) have been shown to exert effects on both the left and right heart. With increasing negativity of intrathoracic pressure on inspiration, venous return increases, at least up to the point at which excessive negative pressure causes collapse of the veins entering the thorax, especially under conditions in which inspiration is prolonged. On the other hand, increasing negativity of intrathoracic pressure also means increased transmural pressure across the left ventricle, and, because of limited space within the pericardium, increased right atrial and ventricular filling will compromise left ventricular expansion (19). Both of these latter influences would impede left ventricular stroke volume and CO. In the healthy heart, preload effects are usually expected to dominate the (net) effect of changing intrathoracic pressures on stroke volume,
but, during strenuous exercise, several additional factors arise that may facilitate or override the effects of a changing intrathoracic pressure per se. These factors include 1) the "peripheral pump" provided by contracting skeletal muscles, which is important, especially in strenuous exercise, in enhancing venous return from the legs (21); 2) the large swings in lung volume that will influence the compliance of the intrathoracic vasculature (24); and 3) reduced systemic venous compliance because of high levels of sympathetic efferent output during exercise. Furthermore, very large negative and positive swings in intrathoracic pressure occur with inspiration and expiration during strenuous exercise, and it is difficult to predict what the net effect of the opposing influences would be on stroke volume in the steady state.

Given our finding of reduced stroke volume with respiratory muscle unloading during maximal exercise, we would speculate that the less negative pleural pressure during inspiration (relative to control), thereby resulting in a net reduction in stroke volume and CO in the steady state. Additional mechanical influences that might have affected stroke volume during respiratory muscle unloading via PAV would include 1) the less positive pleural pressure during inspiration reduced venous return (relative to control), thereby resulting in a net reduction in stroke volume and CO in the steady state. Additional mechanical influences that might have affected stroke volume during respiratory muscle unloading via PAV would include 1) the less positive pleural pressure during inspiration, which may have aided left ventricular filling; and 2) the relatively small but consistent increase in pulmonary vascular resistance, which would increase afterload on the right ventricle. Given the relatively small change in Ppa values, we think that these possibilities are highly unlikely (22). There are some limited, indirect data that support our findings and interpretation with unloading, including the higher venal caval flow rate observed during inspiration compared with expiration at both rest and mild exercise in supine humans (27), and the decrease in stroke volume and CO observed in healthy humans at rest when intrathoracic pressure was increased via continuous positive airway pressure (4, 15). Conversely, during mild exercise, Giesbricht et al. (6) found no effect of unloading (with PAV) or elastic loading on breath-by-breath VO2, which probably also reflected an unchanging CO.

Our reduced stroke volume during unloading was also not predictable from the lack of effect of inspiratory resistive loading on stroke volume and CO that we observed at VO2max (see Fig. 5). This lack of effect of further negativity in pleural pressure during inspiration may mean that the extreme negative pressure incurred during loading was beyond the level at which venous return would be enhanced (24). Alternatively, we may have simply reached the limits of ventricular expansion during diastole imposed by the pericardium (26). In either case, stroke volume and CO would be independent of further reductions in pleural pressure under control conditions at VO2max. We also note that respiratory muscle loading reduced inspiratory pleural pressure but did not change expiratory pressures. If expiratory pressure had been increased (as sometimes occurs normally with increasing expiratory flow resistance during strenuous exercise), stroke volume may actually have fallen during maximal exercise.

In summary, our findings show a clear, consistent, and substantial effect of respiratory muscle unloading on reducing stroke volume and CO at maximal exercise, which we speculate may be due both to a reduced metabolic requirement and to the effects of a less negative pleural pressure on venous return. Certainly, more direct testing is needed to address these mechanisms. Perhaps the use of direct visualization techniques to obtain a beat-by-beat time course of change in stroke volume with unloading during maximal and submaximal exercise would provide a more definitive test of the effect of changes in pleural pressure per se.

Respiratory muscle work and CO distribution. Our present results, when combined with our previous
thermodilution measurements of $Q_{\text{legs}}$ (8), permit us to address for the first time the effects of respiratory muscle work on CO and its distribution during maximal exercise. We summarize the key findings in Fig. 6, which shows the average effects on $O_2$ transport and uptake, of the increases and reductions in the Wb by $\pm 50\%$ and also shows the extrapolation of these unloading effects to a zero Wb, based on the regression lines developed from data over the range of 25–75% reductions in the Wb (see Fig. 2 and Ref. 8). Note that, under control conditions with a maximal CO of 26.5 l/min and $V_O_2$ of 4.40 l/min, 77% of CO was distributed to working locomotor muscles, and $a-vDO_2$ across the legs and across the whole body exceeded 85–90% of $O_2$ extraction. With an increased work of inspiration (greater than control), CO remained unchanged, whereas leg vascular resistance increased and $Q_{\text{legs}}$ fell (secondary to decreased leg vascular conductance), resulting in a substantial reduction in the fraction of CO distributed to working limbs (8). $O_2$ extraction across the legs was unchanged, and therefore a substantial reduction occurred in leg $V_O_2$. However, with respiratory muscle unloading, CO and total $V_O_2$ were reduced, and $Q_{\text{legs}}$ and $V_O_2$ were increased, secondary to decreased leg vascular resistance. Thus unloading of the respiratory muscles resulted in a substantial increase in the fraction of total CO distributed to leg muscles and in the fraction of total $V_O_2$ consumed by the legs.

The present study of respiratory muscle loading and unloading effects on total CO helps to explain some of the effects of respiratory muscle work on limb blood flow previously reported (8). First, the previously observed increases and decreases in $Q_{\text{legs}}$ with unloading and loading, respectively, are not attributable to coincidental changes in total CO (which fell with unloading and was unchanged with loading). Thus these data support our previous contention that a change in the Wb during exercise caused local reflex vasodilation or vasoconstriction of working limb vasculature, presumably mediated by a changing, sympathetic efferent output (8). Second, the fall in $Q_{\text{legs}}$ with respiratory muscle loading was almost double the increase in $Q_{\text{legs}}$ with unloading (see Fig. 6), and this difference may be attributable to the fact that CO was maintained with respiratory muscle loading but fell substantially with respiratory muscle unloading. Thus, with respiratory muscle unloading, the reflex vasodilation in leg muscle resulted in relatively small increases in blood flow, in part because the total “available” blood flow was markedly reduced.

Finally, Fig. 7 shows the estimated distribution of total CO to respiratory and to leg locomotor muscles under physiological control conditions at $V_O_2_{\text{max}}$. The mean value shown for $Q_{\text{legs}}$ (20.3 $\pm$ 0.5 l/min) is the measured value with the use of the thermodilution technique obtained under control conditions at $V_O_2_{\text{max}}$ (see Fig. 6; Ref. 8). This value is labeled as “leg” blood flow, but we are uncertain whether this measurement includes blood flow to all limb musculature actually involved in the exercise. The value for respiratory muscle blood flow (4.2 $\pm$ 0.1 l/min) is taken from the reduction in CO observed between control and unloaded conditions and extrapolated to zero levels of Wb (see Fig. 6). Thus these values would mean that, of the mean maximal 26.5 l/min CO in our subjects, 77% of this total was directed to working legs, 16% to the respiratory muscles, and 7% to other metabolically active tissues. This derived 7% estimate appears to be low, given the mean of 9% of CO estimated by others as the minimum blood flow required by skin, heart, brain,
V̇E values of 113–185 l/min and was 14–15% of and blood flow to the diaphragm (on a per-weight basis). CO was directed to “inspiratory and expiratory” muscles, infused microspheres showed that muscle blood flow at maximal exercise with the use of the Wb at maximal exercise.

significant expiratory flow limitation, and high levels of nonskeletal muscle tissues (Q̇_{other}; 7–9%) represents values based reported that the V̇O₂ of respiratory muscles aver-

by healthy subjects during maximal exercise. They spiratory muscle recruitment patterns experienced subjects, Aaron et al. (1) mimicked the Wb and re-

increased V̇E to 127–193 l/min over a 4-min period in humans. Anholm et al. (3) increased V̇E to 127–193 l/min over a 4-min period in resting humans and observed increases of 4.3 ± 1.0 l/min in CO and 411 ± 92 ml/min in V̇O₂. Also in resting subjects, Aaron et al. (1) mimicked the Wb and respiratory muscle recruitment patterns experienced by healthy subjects, during maximal exercise. They reported that the V̇O₂ of respiratory muscles averaged almost 400 ml/min (or 10% of total V̇O₂max) at V̇E values of 113–185 l/min and was 14–15% of V̇O₂max. In several of the subjects with high levels of V̇E, significant expiratory flow limitation, and high levels of the Wb at maximal exercise.

Direct measurement, in the pony, of respiratory muscle blood flow at maximal exercise with the use of infused microspheres showed that −16% of the total CO was directed to “inspiratory and expiratory” muscles, and blood flow to the diaphragm (on a per-weight basis) exceeded that in limb locomotor muscles (11). Similar studies in pigs and rats also showed substantial exercise-induced increases in diaphragm and expiratory muscle blood flow but not to the same extent as in the pony (10, 14). Of course, these anatomic studies of blood flow distribution do not consider whether these conventionally designated inspiratory and expiratory muscles may take on locomotor and/or postural stabilization roles during exercise or whether traditionally nonrespiratory muscles may assume some ventilatory role during exercise, especially in running quadrupeds (2). Furthermore, the studies of hyperpnea in resting humans probably do not precisely mimic the patterns of respiratory muscle recruitment experienced during exercise, even when the total Wb is similar (1). Also, because the subjects’ locomotor muscles are at rest in these experiments, there is no “competition” for blood flow distribution between limb and respiratory muscles (8). Thus our present approach of using respiratory muscle unloading during exercise may represent the most physiological method to date to quantify the blood flow requirements of the respiratory muscle work during exercise and its effects on blood flow distribution. In summary, given the reasonably close agreement among findings obtained by three quite different approaches and across species (1, 10, 11, 14), we believe it is not unreasonable to conclude that respiratory muscle work at maximal exercise requires an average of 14–16% of the total CO as estimated by our extrapolation of measured values and, furthermore, that reflex effects on Q̇_{legs} associated with respiratory muscle work at V̇O₂max are sufficient to cause changes of up to 20% in the proportion of the total CO made available to working legs (see Fig. 6).

How generalizable are these findings beyond our specific experimental design? First, we emphasize that our data were obtained in highly fit young male subjects at greater than normal V̇O₂max. Our previous study of these types of fit subjects showed that they commonly experienced high ventilatory outputs, significant expiratory flow limitation with increased end-expiratory lung volume during strenuous and maximal exercise, use of up to 90–95% of their inspiratory muscle capacity for pressure generation, and exponential increases in the O₂ cost of breathing as exercise intensity increased from strenuous through maximal levels (1, 9). Accordingly, we would expect the blood flow requirements of the respiratory muscles at maximal exercise as presently reported to represent maximal values in healthy young men. Other subjects or conditions in which we would also expect a high Wb with similar substantial cardiovascular consequences would include elderly healthy fit subjects (9) and young fit female subjects (12), both of whom show excessive flow limitation and/or ventilatory requirements during moderate-to-strenuous exercise. Similarly, strenuous exercise in environments with added ventilatory stimuli such as hypoxia or heat would also be expected to require high levels of ventilatory work and to impose substantial cardiovascular consequences. On the other hand, we do not know how the amount of reflex vasoconstriction
influenced by respiratory muscle work during maximal exercise may differ among subjects and conditions. For example, the amount of sympathetically induced reflex vasoconstriction in response to isometric exercise has recently been shown to be reduced by physical training (13, 25). Whether the ventilatory load in any of these conditions is ever sufficient to cause measurable effects on CO or limb vascular resistance during submaximal exercise remains untested.

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