Influence of respiratory muscle work on $V_O^2$ and leg blood flow during submaximal exercise

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The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Wetter, Thomas J., Craig A. Harms, William B. Nelson, David F. Pegelow, and Jerome A. Dempsey. Influence of respiratory muscle work on $V_O^2$ and leg blood flow during submaximal exercise. J. Appl. Physiol. 87(2): 643–651, 1999.—The work of breathing ($W_b$) normally incurred during maximal exercise not only requires substantial cardiac output and $O_2$ consumption ($V_O^2$) but also causes vasoconstriction in locomotor muscles and compromises leg blood flow ($Q_{leg}$). We wondered whether the $W_b$ normally incurred during submaximal exercise would also reduce $Q_{leg}$. Therefore, we investigated the effects of changing the $W_b$ on $Q_{leg}$ via thermodilution in 10 healthy trained male cyclists (maximal $V_O^2$ ($V_O^{2max}$) = 59 ± 9 ml·kg$^{-1}$·min$^{-1}$) during repeated bouts of cycle exercise at work rates corresponding to 50 and 75% of $V_O^{2max}$. Inspiratory muscle work was 1) reduced 40% with a proportional-assist ventilator, 2) not manipulated (control), or 3) increased 61 ± 8% by addition of inspiratory resistive loads. Increasing the $W_b$ during submaximal exercise caused $V_O^2$ to increase; decreasing the $W_b$ was associated with lower $V_O^2$ ($\Delta V_O^2 = 0.12$ and 0.21 l/min at 50 and 75% of $V_O^{2max}$, respectively, for ~100% change in $W_b$). There were no significant changes in leg vascular resistance (LVR), norepinephrine spillover, arterial pressure, or $Q_{leg}$ when $W_b$ was reduced or increased. Why are LVR, norepinephrine spillover, and $Q_{leg}$ influenced by the $W_b$ at maximal but not submaximal exercise? We postulate that at submaximal work rates and ventilation rates the normal $W_b$ required makes insufficient demands for $V_O^2$ and cardiac output to require any cardiovascular adjustment and is too small to activate sympathetic vasoconstrictor efferent output. Furthermore, even a 50–70% increase in $W_b$ during submaximal exercise, as might be encountered in conditions where ventilation rates and/or inspiratory flow resistive forces are higher than normal, also does not elicit changes in LVR or $Q_{leg}$.

Reducing the work of breathing ($W_b$) at maximal exercise by unloading the respiratory muscles via proportional-assist ventilation (PAV) is associated with decreased leg vascular resistance (LVR) and increased leg blood flow ($Q_{leg}$) and leg $O_2$ consumption ($V_O^2$); loading respiratory muscles by adding inspiratory resistance has the opposite effect (7). This vasodilation of working limb vasculature when the respiratory muscles are unloaded at maximal exercise occurs despite a fall in cardiac output (CO), whereas respiratory muscle loading does not alter CO (8). Presumably, at maximal exercise, where further increases in CO are limited, a competition for blood flow among different skeletal muscle groups exists, such that respiratory muscle blood flow may increase at the expense of blood flow to working limb muscles. The important physiological message from these unloading experiments is that the $W_b$ normally incurred during maximal exercise causes vasoconstriction in working leg muscles and decreases $Q_{leg}$.

Our present study asked whether the $W_b$ normally incurred during submaximal exercise would elicit significant changes in $V_O^2$, $Q_{leg}$, and LVR. To this end, we used the thermodilution technique at two submaximal exercise intensities during control ventilation and unloading of the respiratory muscles to repeatedly measure $Q_{leg}$.

There are many conditions where the $W_b$ is increased during submaximal exercise in the healthy subject, such as with aging, prolonged exercise, or environmental hypoxia, and also in patients with lung or cardiovascular disease (4, 6, 11, 24). Therefore, we also increased $W_b$ by adding inspiratory resistances during submaximal exercise to determine whether increased work of the respiratory muscles would elicit a vasoconstrictor influence on limb muscle vasculature under conditions where CO was not limited. These effects of unloading and loading the respiratory muscles during submaximal exercise are contrasted with the effects determined during maximal exercise.

METHODS

Subjects. Ten male cyclists (nonsmoking, competitive) with resting pulmonary function within normal limits were recruited to participate in the 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 29.7 ± 1.3 (SE) yr, height 182.7 ± 0.9 cm, weight 76.7 ± 2.5 kg, and maximal $V_O^2$ ($V_O^{2max}$) 59.0 ± 8.8 ml·kg$^{-1}$·min$^{-1}$.

Pressure and gas measurements. During all tests the raw data were recorded on an eight-channel Hewlett-Packard tape recorder, Gould chart recorder, and computer for subsequent analysis. Flow rates, esophageal pressure, $V_O^2$, and $CO_2$ production were measured using equipment and techniques previously reported (2, 12). $W_b$ was defined as the product of peak inspiratory esophageal pressure and breathing frequency. This measurement yielded results, when expressed as percentage of control values, similar to those from the integrated area of the pressure-volume loop (7). This index of $W_b$ was chosen over the previously used pressure-volume loop estimation, because hysteresis in some of the unloaded loops at these submaximal workloads made calculations of area difficult to interpret.
Inspiratory unloading and loading. A feedback-controlled PAV (Winnipeg) was used to reduce the work of the inspiratory muscles during exercise (26). Briefly, subjects breathed through a two-way low-resistance non-rebreathing valve (7200 series, Hans Rudolph) that was connected on the inspiratory side to the PAV. The PAV develops pressure in proportion to inspiratory airflow and volume, and the level of assist can be adjusted separately 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. The amount of assist was set at a level at which each subject felt comfortable for each workload, 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, resistive loads consisting of mesh screens and rubber stoppers with various-sized orifices were added to the inspiratory side; these resulted in resistances of 3–10 cmH₂O ·l⁻¹ ·s at the flow rates generated during the cycle exercise. Resistances were selected for each individual and at each work rate and increased the W₀ above control levels by 79 ± 5 and 58 ± 6% at 50 and 75% of V˙O₂max, respectively. In 7 of 10 subjects, slightly smaller resistive loads were applied during additional trials; these increased the W₀ by 58 ± 16 and 37 ± 10% at 50 and 75% of V˙O₂max respectively. Subjects participated in practice sessions to familiarize themselves with the inspiratory loads.

Q˙leg measurements. Q˙leg and leg V˙O₂ were measured using the techniques previously reported (7). A 4.0-Fr catheter, 40 cm long, with 10 side ports, for cold saline infusion (Royal Flush II Nylon, Cook, Bloomington, IN) was introduced percutaneously into the right femoral vein 2 cm below the inguinal ligament and advanced ~7 cm toward the knee. A second identical catheter was advanced from near the same location proximally toward the heart ~8 cm into the same femoral vein. A thin (0.64-mm-diameter) Teflon-coated thermocouple (model 1T-18, Physiostemp Instruments, Clifton, NJ) was inserted through this catheter, with the tip extending ~1 cm beyond the catheter. The placement of the catheter and thermocouple was checked at rest by infusion of 20 ml of saline to produce a 0.5°C deflection in blood temperature and was not changed between trials of exercise. Assumptions regarding this method have been discussed previously (7, 16).

Q˙leg was calculated on the basis of thermal-balance principles described by Andersen and Saltin (3).

Subsequent to placement of the leg catheters, a 20-gauge arterial catheter (Arrow) was inserted percutaneously into the radial artery of the left arm under local 1% lidocaine arterial catheter (Arrow) was inserted percutaneously into the right femoral vein 2 cm below the inguinal ligament and advanced ~7 cm toward the knee. A second identical catheter was advanced from near the same location proximally toward the heart ~8 cm into the same femoral vein. A thin (0.64-mm-diameter) Teflon-coated thermocouple (model 1T-18, Physiostemp Instruments, Clifton, NJ) was inserted through this catheter, with the tip extending ~1 cm beyond the catheter. The placement of the catheter and thermocouple was checked at rest by infusion of 20 ml of saline to produce a 0.5°C deflection in blood temperature and was not changed between trials of exercise. Assumptions regarding this method have been discussed previously (7, 16).

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Subsequent to placement of the leg catheters, a 20-gauge arterial catheter (Arrow) was inserted percutaneously into the radial artery of the left arm under local 1% lidocaine anesthesia for arterial blood sampling. Leg V˙O₂ was calculated as the product of radial arterial-femoral venous O₂ content and Q˙leg (Fick equation). Q˙leg data and leg V˙O₂ are presented as twice the calculated value to represent both exercising legs. The arterial-femoral venous O₂ content was divided by arterial O₂ content to give O₂ extraction. LVR was calculated as the ratio of mean arterial pressure (MAP) to Q˙leg (1, leg).

Blood-gas measurements, blood pressure, and blood lactate. Samples (3–10 ml) of arterial and venous blood were drawn anaerobically over 10–20 s during each trial for measurement of PO₂, PCO₂, and pH with a blood-gas analyzer calibrated with tonometered blood (model ABL300, Radiometer) and measurement of O₂ saturation and Hb with a CO-oximeter (model OSM 3, Radiometer). Blood gases were corrected for temperature changes during exercise by measurement with a thermocouple placed intranasally into the lower third of the esophageal lumen (model 6500, Mon-a-Therm) for arterial blood temperature and from the femoral thermocouple for venous temperature. Arterial and femoral venous blood pressures were measured with pressure transducers (model P10EZ, Ohmeda) attached to the respective arterial and venous lines. Blood lactate concentration was analyzed by means of a lactate analyzer (model 1500 Sport, Yellow Springs Instrument). Hematocrit was determined by microcentrifuge. Norepinephrine spillover technique. Plasma epinephrine, norepinephrine (NE), and dopamine were determined by a high-pressure liquid chromatography method with electrochemical detection. The rate of spillover of NE into plasma was determined as previously reported using blood flow rates, hematocrit, the difference in NE concentration between femoral venous and arterial plasma, and the fractional extraction of epinephrine (22).

Experimental protocol. Each subject completed a progressive incremental V˙O₂max exercise test on a cycle ergometer, as previously described (7). The mean V˙O₂max was 59.0 ± 8.8 ml ·kg⁻¹ ·min⁻¹ (range 48–73 ml ·kg⁻¹ ·min⁻¹). From the V˙O₂max data, workloads for each subject were selected to elicit 50 and 75% of V˙O₂max.

On a separate day, after placement of the catheters and after a sufficient warm-up period, subjects completed two 15–20 min exercise bouts at 50% of V˙O₂max, followed by two 15 min bouts at 75% of V˙O₂max. Each bout was separated by a rest period of ~10–15 min. During each fixed work rate (50 and 75% of V˙O₂max) three or four continuous 5 min periods of control (no ventilatory intervention), inspiratory resistive loading, or unloading were applied, with periods of control and loaded breathing combined in one bout and control and unloaded breathing combined in the other (the ventilatory interventions were randomized). Thereafter, 7 of the 10 subjects, two additional exercise bouts at 50% of V˙O₂max were followed by two bouts at 75% of V˙O₂max. These trials were similar to those described above, except the inspiratory resistive load was decreased slightly during the period of loaded breathing in these later bouts. Within each 5 min period the sequence of measurements was as follows: Q˙leg at 2 min 45 s; blood sampling, esophageal, and femoral venous temperatures at 3 min 55 s; femoral venous pressure at 4 min 15 s; and a second Q˙leg at 4 min 35 s. All other measurements were recorded continuously; values reported and used for calculations (including arterial and esophageal pressures and V˙O₂) were taken at the same time as the Q˙leg measurements.

Changes in Vt were minimized during unloading breathing trials via visual feedback from an oscilloscope marked at control Vt levels, and changes in breathing frequency were minimized during loaded breathing trials via auditory feedback from a metronome set at control breathing frequency. This was done for all exercise bouts at 75% of V˙O₂max. During some of the bouts of unloaded and loaded breathing at 50% of V˙O₂max, subjects were allowed to self-select Vt and breathing frequencies, to whatever felt comfortable. Aside from slight changes in breathing frequency and Vt, this had no effect on the W₀, V˙O₂, Q˙leg or LVR; thus these trials were combined with the other unloaded and loaded breathing trials and analyzed together.

Statistical analysis. Relationships between W₀ and the dependent variables under the three conditions, i.e., control, inspiratory muscle load, and inspiratory muscle unload at each of the two work rates (50 and 75% of V˙O₂max), were determined from simple linear regression. Separate one-way ANOVAs with repeated measures were used to determine treatment differences among group mean values across the three conditions within each exercise level. Tukey’s post hoc
analysis was used to determine where the differences existed. Significance was set at $P < 0.05$.

RESULTS

Figure 1 is a typical example of the multiple measurements made for $Q_{\text{leg}}$, MAP, and LVR plotted vs. $W_b$ in one subject at both submaximal work rates. Regression lines through the individual trials are also displayed. The total number of trials (trial = 2.5 min of leg cycling during which 1 $Q_{\text{leg}}$ measurement was made) for each subject was 25 ± 2 at 50% of $V_{\text{O}_2\text{max}}$ (range 16–28) and 20 ± 2 at 75% of $V_{\text{O}_2\text{max}}$ (range 12–24), and these were roughly divided as 1:4 unloaded, 1:2 control, and 1:4 loaded inspiration.

Using the approach displayed in Fig. 1, we present our findings concerning the effects of changing the $W_b$ on several variables of O$_2$ transport by showing regression lines through the absolute values for each subject and indicating whether the slopes of these lines are significantly different from zero. In addition, the mean values of each variable for each of the three specific conditions (inspiratory unloading, control, or inspiratory loading) and for each work rate are presented in Tables 1 and 2.
Table 1. Effect of increasing and decreasing Wb at 50% of VO2\text{max} on ventilation, O2 transport, VO2, and LVR

<table>
<thead>
<tr>
<th></th>
<th>Inspiratory Unload</th>
<th>Control</th>
<th>Inspiratory Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wb, %control</td>
<td>62 ± 8*</td>
<td>100</td>
<td>171 ± 10*†</td>
</tr>
<tr>
<td>P1, eGPEAK, mmH2O</td>
<td>–15.6 ± 1.24*</td>
<td>–18.49 ± 1.19</td>
<td>–34.87 ± 1.48†</td>
</tr>
<tr>
<td>Vt, l/min</td>
<td>78.5 ± 6.4*</td>
<td>67.9 ± 3.5</td>
<td>57.3 ± 2.5*</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>27.4 ± 2.1</td>
<td>28.3 ± 2.2</td>
<td>24.6 ± 1.4†</td>
</tr>
<tr>
<td>VT, liters</td>
<td>2.95 ± 0.17*</td>
<td>2.47 ± 0.12</td>
<td>2.39 ± 0.13†</td>
</tr>
<tr>
<td>T/TT</td>
<td>0.44 ± 0.02</td>
<td>0.47 ± 0.01</td>
<td>0.59 ± 0.01†</td>
</tr>
<tr>
<td>Qleg, l/min</td>
<td>11.60 ± 0.50</td>
<td>11.48 ± 0.50</td>
<td>11.41 ± 0.47</td>
</tr>
<tr>
<td>(a-fv)DO2, ml/dl</td>
<td>15.42 ± 0.31</td>
<td>15.29 ± 0.34</td>
<td>15.06 ± 0.35</td>
</tr>
<tr>
<td>LegO2 extraction, %</td>
<td>80.2 ± 1.2*</td>
<td>79.3 ± 1.3</td>
<td>79.7 ± 1.3</td>
</tr>
<tr>
<td>Leg VO2, l/min</td>
<td>1.76 ± 0.08</td>
<td>1.73 ± 0.09</td>
<td>1.68 ± 0.08</td>
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<tr>
<td>VO2max, l/min</td>
<td>2.24 ± 0.08</td>
<td>2.28 ± 0.07</td>
<td>2.36 ± 0.08†</td>
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<tr>
<td>Leg VO2/VO2max, %</td>
<td>79.0 ± 3.6</td>
<td>75.6 ± 2.3</td>
<td>70.7 ± 2.0†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>126 ± 3</td>
<td>126 ± 3</td>
<td>129 ± 3†</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>105.6 ± 3.5</td>
<td>104.3 ± 2.9</td>
<td>102.3 ± 2.9†</td>
</tr>
<tr>
<td>LVR, mmHg1·l·min</td>
<td>18.4 ± 0.7</td>
<td>18.4 ± 0.7</td>
<td>18.0 ± 0.6</td>
</tr>
<tr>
<td>NE spillover, ng/min</td>
<td>1.186 ± 0.196</td>
<td>1.423 ± 0.31</td>
<td>1.648 ± 0.30</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 10. Subjects cycled at a work rate of 170 ± 7 W. In 7 subjects, 2 different inspiratory muscle loads were applied at each work rate. Work of breathing (Wb) was changed by –20% but was not significantly different between these 2 ventilatory loads. Because analyzing these loads separately had no significant impact on the findings, they are combined in Tables 1 and 2. P1, eGPEAK: peak inspiratory esophageal pressure; Ve, minute ventilation; f, breathing frequency; VT, tidal volume; T/TT, ratio of inspiratory time to total time; Qleg, leg blood flow; (a-fv)DO2, arterial-femoral venous O2 difference; VO2, O2 uptake; VO2max, maximal VO2; MAP, mean arterial pressure; LVR, leg vascular resistance; NE, norepinephrine.* Significantly different from control; †significantly different from inspiratory unload, P < 0.05.

Wb and minute ventilation. Estimates of Wb using pressure-volume loops resulted in values of 98 and 219 J/min for the control trials at 50 and 75% of VO2\text{max}, respectively (not shown). At both work rates, peak inspiratory esophageal pressures were significantly increased (less negative) with unloading and significantly decreased (more negative) with loading compared with control values. Inspiratory muscle unloading reduced Wb to 62 ± 8 and 58 ± 4% of control at 50 and 75% of VO2\text{max}, respectively, whereas with the inspiratory resistive loads Wb was increased to 171 ± 10% of control at 50% of VO2\text{max} and 151 ± 5% at 75% of VO2\text{max} (Tables 1 and 2).

Minute ventilation was significantly higher for unloading and lower for loading than for control at both exercise intensities (Tables 1 and 2). This was due, in large part, to slight increases in VT for unloading and slight decreases in breathing frequency for loading. The ratio of inspiratory time to total time was significantly higher with loading than for control or with unloading at 50 and 75% of VO2\text{max}.

Blood gases. During control conditions, arterial and femoral venous O2 saturations were 96.0 ± 0.1 and 25.1 ± 5.3% at 50% of VO2\text{max} and 95.2 ± 0.3 and 17.9 ± 3.7% at 75% of VO2\text{max}; arterial PO2 and Pco2 were 92.3 ± 2.0 and 39.4 ± 0.8 Torr at 50% of VO2\text{max} and 88.0 ± 2.3 and 38.1 ± 1.2 Torr at 75% of VO2\text{max}; arterial and femoral venous pH were 7.40 ± 0.01 and 7.30 ± 0.01 at 50% of VO2\text{max} and 7.38 ± 0.01 and 7.26 ± 0.01 at 75% of VO2\text{max}; arterial lactate was 1.34 ± 0.25 mM at 50% of VO2\text{max} and 2.75 ± 0.49 mM at 75% of VO2\text{max}. Arterial O2 content averaged 19.3 ml/dl at both work rates, whereas femoral venous O2 content was 5.0 ml/dl at 50% of VO2\text{max} and decreased to 3.7 ml/dl at 75% of VO2\text{max}. Arterial and femoral venous blood-gas values with the respiratory muscles loaded or unloaded did not differ from those during control.

Effect of Wb on total VO2. Figure 2 shows individual subject regression lines for total VO2 (VO2\text{tot}) vs. Wb. At 50% of VO2\text{max}, 5 of 10 subjects had a significant positive slope (P < 0.05). At 75% of VO2\text{max}, 6 of 10 subjects had significant positive slopes. Combining the individual data revealed that, for a 100% change in Wb (the approximate difference between unloaded and loaded conditions), VO2 would change by 4.6 and 6.0% at 50 and 75% of VO2\text{max}, respectively (P < 0.001).

Effects of changing Wb on O2 transport. Qleg increased in all subjects from a mean of 11.5 l/min at 50% of VO2\text{max} to 16.6 l/min at 75% of VO2\text{max} (Tables 1 and 2). Figure 3 shows individual subject regression lines for Qleg vs. Wb. None of the slopes of these regressions were significant, although in two subjects at 75% of VO2\text{max} the negative slopes approached significance (P < 0.01). Mean Qleg data were not different between respiratory muscle loading conditions at 50% of VO2\text{max}, but a trend for Qleg to decrease with increased Wb was evident by a significant decrease in Qleg (0.54 l/min, P < 0.05) for loaded vs. unloaded conditions at 75% of VO2\text{max} (Table 2).

During control conditions, MAP increased from 104 to 109 mmHg with increasing exercise intensity. At each exercise intensity, mean values for MAP did not differ by > 3 mmHg between respiratory muscle loading conditions (Tables 1 and 2). Several individuals showed slight decreases in MAP with increased Wb; these were always ≤ 5 mmHg (Fig. 4). Mean femoral venous pressure was increased 5–8% with unloading and reduced 4–7% with loading compared with control.

LVR at either exercise intensity did not differ with changes in Wb; there were no significant slopes for individual subjects at either work rate (Fig. 5); this was
true whether MAP or (MAP – mean femoral venous pressure) was used in the calculation for LVR.

Individual regressions for heart rate (HR) vs. \( \dot{W}_b \) showed significant positive slopes for two subjects at 50% of \( \dot{V}O_2_{\text{max}} \) and for three subjects at 75% of \( \dot{V}O_2_{\text{max}} \) (1 subject had a significant negative slope at 75% of \( \dot{V}O_2_{\text{max}} \)). Mean HR was significantly higher (3 beats/min) for loaded than for unloaded and control ventilation at 50% of \( \dot{V}O_2_{\text{max}} \), whereas at 75% of \( \dot{V}O_2_{\text{max}} \) the differences were not significant (Tables 1 and 2).

Given the small or absent changes in \( Q_{\text{leg}} \) or arterial-femoral venous \( O_2 \) content with changing \( \dot{W}_b \) at either work rate, leg \( \dot{V}O_2 \) was significantly increased by 4–5% during respiratory muscle unloading and decreased by 4–5% during loading at both work rates (Tables 1 and 2).

Effect of \( \dot{W}_b \) on NE spillover. NE spillover was significantly increased from 50 to 75% of \( \dot{V}O_2_{\text{max}} \) (\( P, 0.01 \) for control conditions, Tables 1 and 2). The increase averaged 91 ± 20% for individual subjects. There was wide variability in NE spillover between subjects, and there was no significant change with changes in \( \dot{W}_b \) at either of the exercise intensities.
control values obtained at maximal exercise with those at submaximal exercise reveals expected increases for \( V_{O2tot} \) and \( Q_{leg} \) in response to increasing leg work rate. LVR was highest at 50% of \( V_{O2max} \), fell substantially at 75% of \( V_{O2max} \), and remained at this low level at maximal exercise. Similarly, NE spillover was lowest at 50% of \( V_{O2max} \), increased at 75% of \( V_{O2max} \), and remained near this level at maximal exercise.

Note that the absolute \( W_b \) during the loaded trials at submaximal exercise was less than the \( W_b \) during control trials at maximal exercise. This occurred even though the relative increase in \( W_b \) with respiratory muscle loading (when expressed as a percentage of control \( W_b \)) was actually greater at submaximal exercise (150–170%) than at maximal exercise (128%). The major differences with changing the \( W_b \) at maximal vs. submaximal exercise are the greater absolute changes in \( W_b \) achieved at maximal exercise and the changes in LVR and NE spillover with unloading and loading respiratory muscles at maximal but not submaximal exercise.

**DISCUSSION**

Summary of findings. We used multiple trials of submaximal exercise and measurements of limb blood flow in 10 subjects, to test the effects of changing the \( W_b \) on LVR, \( Q_{leg} \), and \( V_{O2tot} \). Our findings at these submaximal exercise levels show that \( V_{O2tot} \) increased with increasing \( W_b \) and decreased with decreasing \( W_b \); however, \( Q_{leg} \), LVR, and NE spillover did not change significantly with changing \( W_b \). These findings at submaximal exercise intensities differ from those previously described at maximal exercise, where \( V_{O2tot} \) (and CO) and LVR were affected by changing \( W_b \). We believe that the lack of effect of loading or unloading respiratory muscles on LVR at submaximal exercise is a consequence of too small a load placed on (or removed from) the cardiovascular system to disturb whatever variable(s) activate(s) the sympathetic nervous system to cause vasoconstriction in active locomotor muscle. Furthermore, the large effect of changing the \( W_b \) on LVR (and \( Q_{leg} \)) during exercise at \( V_{O2max} \) is a consequence of the high \( O_2 \) and blood flow demand of the respiratory muscles occurring at a time when total available blood flow is limited. The major physiological implication of the new findings at submaximal exercise is that the normal \( W_b \) incurred at moderate exercise intensities does not contribute to the tonic vasoconstrictor activity present in working leg muscles. Our findings also suggest that even substantial increases in \( W_b \) (at least in the range of 50–70% above normal) will raise whole body \( V_{O2} \) but do not cause alterations in LVR or \( Q_{leg} \) during submaximal exercise.

Sensitivity of measurements. Our protocol involved making multiple \( Q_{leg} \) measurements for each subject. Because we randomly assigned respiratory muscle load and unloading conditions and analyzed within-bout measurements for trends, we are confident that the results are not obscured by time-dependent effects. Previously, at maximal exercise, we also used multiple exercise trials and measurements of \( Q_{leg} \) and demonstrated an ability to detect systematic changes of <10% in \( Q_{leg} \) that corresponded with changes in \( W_b \) even on an individual-subject basis (7). The reproducibility of \( Q_{leg} \) measurements within trials at \( V_{O2max} \) was very good [coefficient of variation (CV) ± 3.9%]. This reproducibility was comparable at 75% of \( V_{O2max} \) (CV ± 5.5% for \( Q_{leg} \) measurements under control conditions) and was lower at 50% of \( V_{O2max} \) (CV ± 9.9%). Thus a relative mean change in \( Q_{leg} \) over the range of the change in \( W_b \) similar to that seen at \( V_{O2max} \) (11%) would have been slightly more difficult to detect at the submaximal work rates.

Effect of changing \( W_b \) on \( V_{O2tot} \). By increasing \( W_b \) at submaximal work rates (50 and 75% of \( V_{O2max} \)), we were able to show a relatively small but significant increase in \( V_{O2tot} \); similarly, by reducing \( W_b \) via PAV, \( V_{O2tot} \) decreased compared with control. Although these changes in \( V_{O2tot} \) are relatively small, they are what would be predicted on the basis of previous measurements of the \( O_2 \) cost of mimicking the mechanics and breathing pattern of exercise hyperpnea in normal subjects at rest (1). Given the regression equation developed by Aaron et al. (respiratory muscle \( V_{O2} = 0.081 + 0.001 \times W_b \), where \( W_b \) is measured from pressure-volume loops and is in l/min), we estimate from our measurements 1) that the total \( O_2 \) cost of breathing at 50 and 75% of \( V_{O2max} \) is 0.18 and 0.30 l/min, respectively and 2) that the \( O_2 \) cost of the change in the \( W_b \) between unloaded and loaded conditions is 0.11 l/min at 50% of \( V_{O2max} \) and 0.20 l/min at 75% of \( V_{O2max} \). These latter estimates were nearly identical to the group mean \( V_{O2tot} \) differences of 0.12 and 0.21 l/min.
found in the current study. On the basis of this same equation, corresponding values at VO2max were estimated to be 0.61 l/min for the total O2 cost of breathing during control conditions and a change in VO2 of 0.54 l/min over the range of Wb between unloaded and loaded breathing.

According to the Fick principle, changes in CO and/or arterial-mixed venous O2 difference would be responsible for the VO2 change with changing Wb during exercise. At maximal exercise, unloading resulted in a decreased stroke volume and CO (HR and arterial-mixed venous O2 difference did not change), which we associated with increases in inspiratory intrathoracic pressure (8). It is also likely during submaximal exercise that our observed decrease in VO2 corresponded with a decrease in CO. With respiratory muscle loading, CO (or VO2tot) did not change at maximal exercise, probably because the limits of the pericardium had been reached (8). At submaximal exercise, loading did increase VO2, and it is likely that stroke volume and CO were also increased by the more negative intrathoracic pressures with loading.

Respiratory muscle work and changes in LVR. Why did adding and removing respiratory muscle work at maximal exercise cause changes in LVR, and why were these changes not seen during the current study at submaximal exercise? Our basic premise during maximal exercise was that the work and/or aerobic status of the respiratory muscles stimulated type III-IV afferents in the diaphragm and other respiratory muscles, which then caused reflex vasoconstriction of limb vasculature during control or loaded conditions and reflex vasodilation with respiratory muscle unloading (9). Indirect evidence in support of this postulate and a discussion of other possible mechanisms (i.e., baroreflexes) were presented previously (7).

Unloading the respiratory muscles. These unloading data are especially important, because they speak directly to the cardiovascular role of respiratory muscle work and/or intrathoracic pressure normally incurred

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Fig. 6. Comparison of VO2tot and Qleg (A) and leg vascular resistance and norepinephrine (NE) spillover (B) with absolute Wb at VO2max, 75% of VO2max, and 50% of VO2max. VO2max data are from Harms et al. (7). Wb for control values at 50 and 75% of VO2max were estimated from pressure-volume loops (as was done for VO2max values); Wb for unloaded and loaded values are based on percent change from control values as estimated by peak inspiratory esophageal pressure × breathing frequency. Five subjects did both studies (Ref. 7 and present study), and 2 others did maximal but not submaximal exercise study; fitness level of these 2 subjects was similar to that of additional 5 subjects who participated in submaximal study. *Significantly different from control (middle values), P < 0.05.
at the various exercise intensities. Why did respiratory muscle unloading result in decreases in LVR at maximal but not submaximal exercise? One possibility is that, during submaximal exercise, tonic vasoconstrictor sympathetic nerve activity to locomotor muscles is not normally present (during control conditions), and thus there would be no activity to relieve with respiratory muscle unloading. This does not appear to be likely, since there is overwhelming evidence that tonic vasoconstrictor activity is present in leg vasculature during moderate exercise (20). Furthermore, in our experiment, under control exercise conditions, we observed a measurable level of NE spillover at 50% of \( V_{\text{O2max}} \) and a 63% increase in this mean level at 75% of \( V_{\text{O2max}} \). In fact, at 75% of \( V_{\text{O2max}} \) the NE spillover approximated that at \( V_{\text{O2max}} \). LVR followed similar trends, showing a decrease from 50 to 75% of \( V_{\text{O2max}} \) and comparable values at 75% of \( V_{\text{O2max}} \) and \( V_{\text{O2max}} \). Accordingly, we would suggest that substantial sympathetic vasoconstrictor activity did indeed exist at these submaximal workloads, which potentially could have been relieved with respiratory muscle unloading. Therefore, we must conclude that in our healthy subjects the work of breathing normally incurred during these submaximal exercise intensities does not contribute to the vasoconstrictor tone present in working locomotor muscles.

Loading the respiratory muscles. Why did additional respiratory muscle loading result in increases in LVR at maximal but not submaximal exercise? Perhaps the load placed on the respiratory muscles at submaximal exercise was simply insufficient to cause a change. Although we did increase the \( W_b \) substantially (50–70%), the absolute increase in \( W_b \) was less than that achieved during maximal exercise. However, even had we increased the \( W_b \) to the same level attained during maximal exercise, it is likely that an increase in \( V_{\text{O2}} \) and CO that would enhance \( O_2 \) transport to meet the increased metabolic requirements of the respiratory muscles would have occurred. This compensatory response at submaximal exercise is different from the case of maximal exercise, where increasing blood flow and \( O_2 \) transport to meet the increased work of the respiratory muscles were not accomplished by an augmented CO (8). Thus, at maximal exercise, increased LVR and diversion of blood flow from working leg muscle was necessary. Our present experimental design did not provide a sufficiently large increase in \( W_b \) during submaximal exercise to distinguish between these possibilities.

Relevance of findings. Our findings are relevant to several conditions in which ventilatory work is increased during submaximal exercise. For example, in elderly fit men, ventilatory work is increased (relative to younger fit men) throughout exercise. This is due to an enhanced ventilatory response to compensate for increased dead space ventilation and possibly the presence of expiratory flow limitation (11). LVR is also increased and \( Q_{\text{leg}} \) is decreased across a range (mild to heavy) of exercise intensities (17). Present findings would not predict that most of this decreased limb flow rate was attributable to increased \( W_b \) at least at work rates up to 75% of \( V_{\text{O2max}} \). We hasten to add that the nature of the increase in ventilatory work is quite different from our experimentally induced increases in \( W_b \), which were purely increased inspiratory flow resistive work. The elderly have increased ventilation rates, expiratory flow limitation, relative hyperinflation, and increased elastic work, all of which may have some reflex influence on sympathetic nerve activity (5, 23).

Our data do not indicate that an abnormally high \( W_b \) during submaximal exercise will never influence LVR or \( Q_{\text{leg}} \). For example, in heart failure patients, exercise hyperpnea is enhanced and peripheral blood flow is reduced. Although a causal link between these two factors has not been established, they have been theoretically linked as parts of one underlying process (4).

In the rat model with myocardial infarction, blood flow to the diaphragm is enhanced and limb muscle blood flow reduced during submaximal exercise (15). A similar scenario might occur with submaximal exercise in healthy subjects during short-term exposure to the hypoxia of high altitude, where, again, hyperventilation and increased ventilatory work are combined with a reduced CO at any given submaximal \( V_{\text{O2}} \) (24, 25). Another exceptional case in this regard may occur in prolonged exercise at fixed, heavy, submaximal work rates, where a time-dependent tachypnea, hyperventilation, expiratory flow limitation, and increased ventilatory work occur and where diaphragmatic fatigue is prevalent (10).

In summary, our present and past results would predict that the normally occurring \( W_b \) with increasing exercise intensity in healthy subjects at sea level would require a progressively greater portion of the increasing CO (and \( V_{\text{O2}} \)) to be directed to respiratory muscles at all work rates; however, these effects of increasing ventilatory work on sympathetic vasoconstrictor outflow and on limb blood flow would not be realized until maximal or at least very near-maximal exercise intensities. Our present findings do not allow us to distinguish between increased ventilatory work per se and a limited blood flow distribution as the primary trigger for increased vasoconstrictor outflow to locomotor muscle.

Hierarchy of muscle blood flow distribution during exercise. Because the diaphragm and accessory respiratory muscles have a high oxidative capacity, their resistance vessels may be especially sensitive to local vasodilator influences (13, 14). The fact that decreases in \( Q_{\text{leg}} \) were observed with addition of respiratory muscle work (7) but not with added arm work (18, 19, 22) was interpreted to mean that, at high-intensity exercise, a hierarchy may exist for blood flow distribution, with respiratory muscles ranking before leg and arm musculature (21). However, our present findings show that changing respiratory muscle work did not cause changes in LVR or \( Q_{\text{leg}} \) during submaximal exercise. Accordingly, respiratory muscles may not rank above limb muscles in terms of vasodilatory sensitivity, and the reason for differences in previous findings may be more related to the different work intensities used...
and the limits to available CO imposed at $V_{O2max}$. A quite different type of hierarchy might exist among the different skeletal muscle vascular beds in terms of their relative propensity to produce and accumulate metabolic end products. The higher oxidative capacity and fatigue resistance of the diaphragm vs. leg vs. arm muscles must maintain a much higher work intensity before incurring sufficient metabolic acidosis to trigger sympathoexcitatory reflexes.

Of course, these suggestions are highly speculative. Given the present background of mostly descriptive data, we now need to reduce the complexity of our experimental paradigm and more thoroughly explore data, we now need to reduce the complexity of our experimental paradigm and more thoroughly explore the type of mechanisms that might underlie these reflex vasoactive effects that arise when competition for the type of mechanisms that might underlie these reflex vasoactive effects that arise when competition for

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