Respiratory muscle work compromises leg blood flow during maximal exercise

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Harms, Craig A., Mark A. Babcock, Steven R. McClaran, David F. Pegelow, Glenn A. Nickele, William B. Nelson, and Jerome A. Dempsey. Respiratory muscle work compromises leg blood flow during maximal exercise. *J. Appl. Physiol.* 82(5): 1573–1583, 1997.—We hypothesized that during exercise at maximal O_2 consumption ($\dot{V}O_{2max}$), high demand for respiratory muscle blood flow ($\dot{Q}$) would elicit locomotor muscle vasoconstriction and compromise limb $\dot{Q}$. Seven male cyclists ($\dot{V}O_{2max}$ 64 ± 6 ml · kg^{-1} · min^{-1}) each completed 14 exercise bouts of 2.5-min duration at $\dot{V}O_{2max}$ on a cycle ergometer during two testing sessions. Inspiratory muscle work was either *1*) reduced via a proportional-assist ventilator, *2*) increased via graded resistive loads, or *3*) was not manipulated (control). Arterial (brachial) and venous (femoral) blood samples, arterial blood pressure, leg $\dot{Q}$ ($\dot{Q}$legs; thermodilution), esophageal pressure, and O_2 consumption ($\dot{V}O_2$) were measured. Within each subject and across all subjects, at constant maximal work rate, significant correlations existed (r = 0.74–0.90; $P < 0.05$) between work of breathing (Wb) and $\dot{Q}$legs (inverse), leg vascular resistance (LVR), and leg $\dot{V}O_2$ ($\dot{V}O_{2legs}$; inverse), and between LVR and norepinephrine spillover. Mean arterial pressure did not change with changes in Wb nor did tidal volume or minute ventilation. For a ±50% change from control in Wb, $\dot{Q}$legs changed 2 l/min or 11% of control, LVR changed 13% of control, and O_2 extraction did not change; thus $\dot{V}O_{2legs}$ changed 0.4 l/min or 10% of control. Total $\dot{V}O_{2max}$ was unchanged with loading but fell 9.3% with unloading; thus $\dot{V}O_{2legs}$ as a percentage of total $\dot{V}O_{2max}$ was 81% in control, increased to 89% with respiratory muscle unloading, and decreased to 71% with respiratory muscle loading. We conclude that Wb normally incurred during maximal exercise causes vasoconstriction in locomotor muscles and compromises locomotor muscle perfusion and $\dot{V}O_2$.

vascular resistance; blood flow; work of breathing; maximal exercise; sympathetic vasoconstriction; autonomic reflexes; sympatholysis

DURING STRENUOUS EXERCISE in humans, when the level of ventilatory requirement is such that severe expiratory flow limitation is realized, the O_2 cost of breathing may approach 15% of total O_2 consumption ($\dot{V}O_{2tot}$) (1). Studies using microsphere techniques for measuring blood flow ($\dot{Q}$) in running quadrupeds (rats, pigs, and ponies) show substantial increases in $\dot{Q}$ to the diaphragm and inspiratory and expiratory muscles, which often approximate the $\dot{Q}$ to locomotor muscles during maximal exercise (4, 11, 13). Theoretically, the metabolic cost of breathing required by the primary respiratory and stabilizing muscles of the chest wall, plus their demand for perfusion to meet this O_2 cost, could limit the $\dot{Q}$ available for locomotor muscles and thereby limit their work output.

To date, the question of "competition" for redistribution of $\dot{Q}$ with added muscle mass has been addressed only during submaximal exercise. Secher et al. (27) determined that adding arm work to legs already exercising at submaximal exercise resulted in reduced $\dot{Q}$ to the legs ($\dot{Q}$legs). They surmised that increased $\dot{Q}$ was made available to the working arms at the expense of $\dot{Q}$legs. However, several recent reports have failed to corroborate these findings (20, 21, 23, 25). In these investigations, when arm work was added to already exercising legs during submaximal exercise, increased sympathetic excitation of the leg vasculature occurred, as evidenced from increased norepinephrine (NE) spillover, but reduced $\dot{Q}$legs did not occur. Perhaps clear, consistent demonstration of $\dot{Q}$ redistribution and local vasoconstriction might only occur when muscle mass is added at truly maximal workloads (WL), at which both cardiac output and the arteriovenous O_2 difference are at maximal levels.

The purpose of this study was to determine whether there is competition for $\dot{Q}$ and $\dot{V}O_2$ between the respiratory muscles and limb locomotor muscles during maximal exercise. We measured $\dot{Q}$, O_2 extraction, and $\dot{V}O_2$ of the maximally exercising limb and observed the effects of alterations in respiratory muscle work during several repeated bouts of maximal exercise. We hypothesized that, with an increased work of breathing (Wb), $\dot{Q}$ would be redistributed to the respiratory muscles from limb locomotor muscles and with decreased work of breathing, greater $\dot{Q}$ and O_2 transport would be made available to limb locomotor muscles. The latter respiratory muscle "unloading" experiments also allowed us to examine the physiological importance to limb $\dot{Q}$ and O_2 transport of the respiratory muscle work normally achieved at maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$).

METHODS

Subjects. Seven male cyclists (nonsmoking; competitive) 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 28.6 ± 3.3 (SD) yr; height 179.3 ± 2.2 cm; and weight 68.9 ± 4.0 kg.

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, flow-volume and esophageal pressure (Pes)-volume relationships, end-expiratory lung volume, $\dot{V}O_{2tot}$, and CO_2 output were measured by using equipment and techniques previously reported (1, 9). Wb was defined as the integrated area of the pressure-tidal volume

(V_T) loop (15). Wb multiplied by the breathing frequency (f) 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 work of breathing by variable amounts (1, 7); thus our measurements report only a conservative estimate of the total amount of work done by the respiratory muscles during exercise and their changes with unloading and loading.

Inspiratory unloading and loading. A feedback controlled "proportional-assist" ventilator (PAV; Winnipeg) 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 (5-liter volume capacity) that 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 each subject can tolerate, as determined from practice sessions before testing. During practice sessions and during the 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, ventilatory loads were added that consisted of mesh screens in the inspiratory line with resistances of 3–5 $cmH_2O \cdot l^{-1} \cdot s$. These resistances were sufficient at the high flow rates achieved in maximal exercise to increase Wb 25–95% above control levels. Subjects participated in practice sessions to familiarize themselves with the inspiratory loads.

$\dot{Q}$ and blood-gas measurements. A 20-gauge arterial catheter (Arrow) was inserted percutaneously in the brachial artery of the left arm under local 1% lidocaine anesthesia for arterial blood sampling. Subsequently, a catheter 1.25 mm in external diameter for cold-saline infusion (DSA 400L, 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 Cook catheter was advanced from near the same location proximally toward the heart ~8 cm into the same femoral vein. A thin (0.64-mm-diam) Teflon-coated thermocouple (IT-18, Physi-temp 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. The placement was not changed between trials of exercise. An assumption is that the placement of the catheter reflects changes occurring only within the exercising leg muscles. Poole et al. (18) have reported that there is <5% contamination of venous blood from saphenous drainage during strenuous exercise.

The constant-infusion thermodilution technique was used to determine $\dot{Q}$legs (2, 18). Saline temperature was measured with a thermocouple at the catheter inlet within 15 cm of the catheter's penetration of the skin. Infusion flows typically were ~190–240 ml/min and were continued for 15–20 s until femoral venous temperature had decreased and stabilized. Infusion rate of saline was measured from timed changes in weight of a 250-ml bag of saline suspended in a plastic bag from a force-displacement transducer. A chart (Gould) recording and computer-analysis output confirmed the constancy of saline infusion rate and enabled the calculation of saline inflow. The thermocouples were attached to junction boxes (TH5, Sensortek), in which analog signals from the junction boxes were recorded on a strip chart (Gould) and computer for timed measurements of saline and blood temperature. This enabled direct observation of changes in temperature that was necessary to ensure stable tracings. Saline infusion rates were sometimes adjusted slightly immediately after the first $\dot{Q}$leg measurement within a trial to ensure a plateau in the femoral venous temperature recordings, because it was difficult to accurately predict the appropriate infusion rate for each subject. Signals from the force transducer and thermocouple junction box were calibrated at the beginning and end of the experiments. $\dot{Q}$leg was calculated on the basis of thermal-balance principles described by Andersen and Saltin (2).

$\dot{V}O_{2legs}$ was calculated as the product of brachial arterial-femoral venous O_2 content [(a-fv)C_{O_2}] and $\dot{Q}$ (Fick equation). $\dot{Q}$legs data and $\dot{V}O_{2legs}$ are presented as twice the calculated value to represent both exercising legs. The (a-fv)C_{O_2} was divided by arterial O_2 content to give O_2 extraction. Leg vascular resistance (LVR) was calculated as the ratio of mean arterial blood pressure to $\dot{Q}$legs.

Blood-gas measurements, blood pressure, blood lactate, and electrolytes. Duplicate 3- to 10-ml samples of arterial and venous blood were drawn anaerobically over 10–20 s during each test for measurement of P_{O_2}, P_{CO_2}, and pH with a blood-gas analyzer calibrated with tonometered blood (ABL300, Radiometer), and of O_2 saturation and hemoglobin with a CO-oximeter (OSM 3, Radiometer). Blood gases were corrected for temperature changes during exercise by measuring with a thermocouple placed intranasally in the esophageal lumen (Mon-a-Therm 6500) for arterial blood temperature and from the femoral venous thermocouple. Blood pressure was measured with an Ohmeda pressure transducer (model P10EZ) attached to the arterial line. Blood lactate concentration was analyzed by means of a YSI lactate analyzer (model 1500 Sport; YSI) and plasma electrolytes (Na^+, K^+, Cl^-) were analyzed by ion-specific electrodes (AVL Electrolyte Analyzer, series 9100). Hematocrit was determined by microcentrifuge.

NE spillover technique. Plasma epinephrine and NE were determined in duplicate by a radioenzymatic assay (5) for the first of each condition (no breathing intervention, inspiratory unload, and inspiratory load). Net overflow of NE from skeletal muscle was calculated, by the Fick principle, from the product of the venoarterial difference in plasma NE concentration and the plasma flow. The rate of spillover of NE into plasma was determined by using the following equation

$$\text{NE spillover} = [(Cv - Ca) + Ca(Epi_e)]LPF$$

where Cv and Ca are plasma concentrations in the femoral vein and artery, respectively, Epi_e is the fractional extraction of epinephrine, and LPF is the leg plasma flow, determined from $\dot{Q}$legs and the hematocrit (25).

Experimental protocols. Subjects initially completed a progressive incremental $\dot{V}O_{2max}$ exercise test on an electromagnetically braked cycle ergometer (Elema, Sweden) beginning at 150 W (~30–40% $\dot{V}O_{2max}$) 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. After a 20-min recovery, subjects cycled to exhaustion at 5–10% above their peak $\dot{W}$L (as determined by the prior progressive test) to verify $\dot{V}O_{2max}$. A plateau (<150 ml) or decrease in $\dot{V}O_2$ was observed for each subject between the final two WL of the incremental $\dot{V}O_{2max}$ test and/or between the final WL of the incremental test and the WL of the repeat

test. The mean $\dot{V}O_{2max}$ was 64.3 ± 5.6 ml·kg^{-1}·min^{-1} (range 55–74 ml·kg^{-1}·min^{-1}).

On separate days, and on placement of the catheters, subjects completed two testing sessions (separated by 2–4 wk). Each session consisted of seven exercise tests (separated by 15–20 min). All tests were performed at a WL that was at (3 subjects; 412 ± 45 W) or near (4 subjects; 398 ± 31 W; >95% $\dot{V}O_{2max}$) their $\dot{V}O_{2max}$ and that could be maintained 2.5–3.0 min (as determined from a separate practice session). The first six tests (2.5 min each) consisted of two bouts with no ventilatory interventions (control), two bouts of inspiratory muscle unloading, and two bouts of inspiratory muscle loading. The first test of each day was a trial with no ventilatory intervention (control), whereas the order of the remaining five bouts was randomized. Subjects first increased work rate progressively to maximum over 30 s, and then, within the subsequent 2.5 min, the sequence of measurements was blood sampling (1:00–1:15 min) followed by simultaneously measured femoral venous $\dot{Q}$ and arterial blood pressure (1:16–1:30 min). This sequence was then repeated (2:00–2:30 min).

The seventh test of each day was a 3-min continuous WL test, consisting of 30 s of progressive increase in work rate to maximum, 1 min of no breathing intervention-1 min of either inspiratory muscle loading or unloading-1 min of no breathing intervention. Blood sampling, $\dot{Q}$leg, and arterial blood pressure measurements were made during the final 30 s of each minute. The rationale for this continuous test was twofold. First, we were interested in the transitions (10–15 s) from control to load/unload and back to control to determine whether the changes in respiratory load transiently affected systemic blood pressure and heart rate. Second, we wished to confirm, by using data obtained during the final 30 s of each min of the 3-min exercise test, whether the change in $\dot{Q}$legs (LVR, $\dot{V}O_{2tot}$) with unloading/loading changed with a changing Wb in a direction similar to the changes seen during the 2.5-min intermittent tests.

Statistical analysis. We wished to determine whether, at exercise requiring $\dot{V}O_{2max}$, significant relationships existed between Wb and the dependent variables under three conditions: control, inspiratory muscle load, and inspiratory muscle unload. Therefore, we computed the best fit regression equations across all exercise trials, first within a single subject and then across all subjects. The software packages were Sigmaplot and SPSS. An analysis of variance was used to determine treatment differences between group mean values under each of the three conditions. Tukey's post hoc test was used to determine where the differences existed. Significance was set at $P < 0.05$.

RESULTS

Table 1 shows the reproducibility of $\dot{Q}$legs, arterial-femoral venous O_2 difference [(a-fv)D_{O_2}], leg $\dot{V}O_2$, and LVR measurements within the 2.5-min trials for all tests and between the first trials (controls) for each subject over both days. The coefficients of variation (CV) were ≤ ± 3.9% for the within-trial measurements and ≤ ± 8.3% for between-trial measurements. No systematic changes (between-group mean values) were found over time within each exercise trial or between trials at the 2.5-min time point ($P > 0.05$).

We present our findings concerning the effects of changing the Wb on several variables of O_2 transport by showing the regression of Wb vs. each variable at $\dot{V}O_{2max}$ *1*) in absolute values for each subject and *2*) as a percentage of control across all subjects. The relationships between the dependent variables and Wb during those 3-min trials in which inspiratory muscles were unloaded or loaded within the trial were similar ($P > 0.05$) to those obtained during the constant-load exercise. Thus the findings from both types of trials were combined to determine the relationships of Wb to several variables of O_2 transport. The group mean changes for each variable measured during inspiratory unloading, control, and inspiratory loading are summarized in Tables 2 and 3.

Wb. Figure 1 depicts a representative pressure-volume loop in one subject from an inspiratory muscle unload, inspiratory muscle load, and control trial at $\dot{V}O_{2max}$. Table 2 shows the average change in Wb, peak inspiratory and expiratory Pes, and ventilatory output achieved with inspiratory unloading and loading. Inspiratory muscle unloading during exercise reduced the Wb by highly variable amounts to average 36.7 ± 26.6% of control, whereas with resistive loads, Wb was increased to 128.2 ± 25.2% from control with all trials combined. Peak inspiratory Pes was reduced 50 ± 3% with inspiratory unloading and increased 28 ± 5% with inspiratory loading. Peak expiratory Pes was reduced 32 ± 4% with inspiratory unloading but was not different from control with inspiratory loading. The difference between peak inspiratory and peak expiratory Pes was 50.3 cmH_2O during control, 29.1 cmH_2O during unloading trials, and 55.2 cmH_2O during loaded

Table 1. *Reproducibility within and between trials at $\dot{V}O_{2max}$*

	Within Same Exercise Trial ($n = 82$)†			Between Days ($n = 28$)*		
	1:30 min	2:30 min	±CV, %	*Day 1*	*Day 2*	±CV, %
$\dot{Q}$legs, l/min	17.9 ± 1.9	18.4 ± 1.1	±3.9	18.7 ± 1.5	18.3 ± 1.3	±3.1
(a-fv)D_{O_2}, ml/dl	18.0 ± 0.9	18.3 ± 0.6	±2.1	18.1 ± 1.2	18.3 ± 1.1	±5.8
$\dot{V}O_{2legs}$, l/min	3.22 ± 0.18	3.37 ± 0.08	±1.9	3.31 ± 0.37	3.34 ± 0.36	±5.9
LVR, mmHg·l^{-1}·min	13.8 ± 1.9	13.6 ± 1.0	±1.8	13.3 ± 1.4	14.1 ± 1.6	±8.3
MAP, mmHg	123.7 ± 3.6	125.2 ± 3.8	±4.1	124.6 ± 4.1	129.9 ± 3.7	±7.9

Values are means ± SE for 7 subjects. n = No. of trials; $\dot{Q}$legs, leg blood flow; (a-fv)D_{O_2}, arterial femoral venous O_2 difference; $\dot{V}O_{2legs}$, O_2 consumption by legs; LVR, leg vascular resistance; MAP, mean arterial pressure. Coefficients of variation (±CV) were determined by computing SD differences between measurements (within or between trials) and dividing by grand mean. *Data for comparison between days were obtained after 2:15–2:30 min of exercise. Data reported here for all between day trials are under control conditions at $\dot{V}O_{2max}$. †Includes all trials during control, unloading, and loading conditions. Subjects were at their maximal work rate for 2.5 min, but this was preceded by 30 s of exercise of gradually increasing intensity leading up to maximal work rate (see METHODS).

Table 2. *Effect of increasing and decreasing work of breathing at $\dot{V}O_{2max}$ on ventilation, blood gases, and electrolytes*

	Inspiratory Assist (36.7 ± 26.6)	Control (98.4 ± 9.3)	Inspiratory Load (128.2 ± 25.2)
Wb, J/min	194.1 ± 26.3*	527.7 ± 23.2	732.9 ± 52.0*
$P_{I,es_{peak}}$, cmH_2O	−14.0 ± 0.6*	−28.1 ± 0.7	−34.0 ± 0.7*
$P_{E,es_{peak}}$, cmH_2O	15.1 ± 0.6*	22.2 ± 0.8	21.2 ± 0.9
$\dot{V}_E$, l/min	156.7 ± 4.5	145.7 ± 6.2	147.6 ± 6.1
f, breaths/min	47.7 ± 2.0	46.6 ± 2.1	47.5 ± 1.8
V_T, liters	3.29 ± 0.15	3.25 ± 0.14	3.13 ± 0.14
Pa_{O_2}, mmHg	94.7 ± 1.1	92.6 ± 1.3	92.5 ± 1.0
Pfv_{O_2}, mmHg	11.6 ± 0.7	11.7 ± 0.9	11.7 ± 0.8
Sa_{O_2}, %	94.7 ± 0.2	94.7 ± 0.1	94.6 ± 0.2
Sfv_{O_2}, %	9.6 ± 0.6	10.4 ± 0.7	10.0 ± 0.6
Pa_{CO_2}, mmHg	37.8 ± 1.9	37.6 ± 1.7	37.6 ± 1.1
Pfv_{CO_2}, mmHg	80.7 ± 1.7	81.3 ± 1.9	80.9 ± 1.7
pH_a	7.294 ± 0.001	7.294 ± 0.010	7.292 ± 0.001
pH_{fv}	7.087 ± 0.011	7.084 ± 0.012	7.095 ± 0.001
$[L]_a$, mM	8.95 ± 0.41	8.84 ± 0.46	8.83 ± 0.33
$[L]_{fv}$, mM	9.48 ± 0.38	9.72 ± 0.32	9.39 ± 0.29
fv-a[L]outflow, mM/min	12.6 ± 1.4	14.6 ± 2.0	11.9 ± 1.1
K_a^+, mmol/l	6.16 ± 0.03	6.06 ± 0.04	6.23 ± 0.04
K_{fv}^+, mmol/l	6.25 ± 0.05	6.17 ± 0.04	6.28 ± 0.05

Values are means ± SE; $n = 7$. Wb, work of breathing; $P_{I,es_{peak}}$, peak inspiratory esophageal pressure; $P_{E,es_{peak}}$, peak expiratory esophageal pressure; $\dot{V}_E$, minute ventilation; f, breathing frequency; V_T, tidal volume; Pa_{O_2}, arterial P_{O_2}; Pfv_{O_2}, femoral venous P_{O_2}; Sa_{O_2}, arterial O_2 saturation; Sfv_{O_2}, femoral venous O_2 saturation; Pa_{CO_2}, arterial P_{CO_2}; Pfv_{CO_2}, femoral venous P_{CO_2}; pH_a and pH_{fv}, arterial and femoral venous pH, respectively; $[L]_a$ and $[L]_{fv}$, arterial and femoral venous lactate concentration, respectively; fv-a[L], femoral venous-arterial lactate; K_a^+ and K_{fv}^+, arterial and femoral venous potassium, respectively; values in parentheses, Wb %control. * Significantly different from control, $P < 0.05$.

Table 3. *Effect of increasing and decreasing $\dot{W}b$ at $\dot{V}O_{2max}$ on O_2 transport, O_2 uptake, and LVR*

	Inspiratory Assist (36.7 ± 26.6)	Control (98.4 ± 9.3)	Inspiratory Load (128.2 ± 25.2)
$\dot{Q}$legs, l/min	19.2 ± 0.3*	18.4 ± 0.3	17.1 ± 0.2*
(a-fv)D_{O_2}, ml/dl	18.1 ± 0.2	18.3 ± 0.2	18.3 ± 0.2
$\dot{V}O_{2legs}$, l/min	3.51 ± 0.07*	3.41 ± 0.10	3.13 ± 0.06*
Ca_{O_2}, ml/dl	20.0 ± 0.2	20.4 ± 0.1	20.0 ± 0.1
Cfv_{O_2}, ml/dl	1.9 ± 0.1	2.1 ± 0.1	2.0 ± 0.1
Leg $\dot{O}_2$ extraction, %	89.8 ± 0.3	90.5 ± 0.5	89.9 ± 0.3
$\dot{V}O_{2tot}$, l/min	3.96 ± 0.13*	4.22 ± 0.10	4.29 ± 0.11
$\dot{V}O_{2legs}/\dot{V}O_{2tot}$, %	88.6 ± 0.7*	80.6 ± 1.0	71.2 ± 1.0*
HR, beats/min	183 ± 2	184 ± 2	184 ± 2
MAP, mmHg	125.9 ± 2.3	125.4 ± 2.5	124.8 ± 2.2
SBP, mmHg	214.2 ± 4.9	218.2 ± 4.0	216.7 ± 3.9
DBP, mmHg	80.5 ± 2.4	81.8 ± 2.3	82.3 ± 2.6
LVR, $mmHg \cdot l^{-1} \cdot min$	13.1 ± 0.3*	13.6 ± 0.4	14.6 ± 0.3*
NE spillover, ng/min	2426.1 ± 191.9	2720.0 ± 183.6	4883.9 ± 233.7*
NE_a, ng/ml	3.67 ± 0.27	3.46 ± 0.31	3.86 ± 0.27
Epi_a, ng/ml	0.93 ± 0.14	0.89 ± 0.13	1.02 ± 0.22

Values are means ± SE; $n = 7$. Ca_{O_2}, arterial O_2 content; Cfv_{O_2}, femoral venous oxygen content; $\dot{V}O_{2tot}$, pulmonary $\dot{V}O_2$; $\dot{V}O_{2legs}$, leg $\dot{V}O_2$; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVR, leg vascular resistance; NE, norepinephrine; NE_a, arterial NE; Epi_a, arterial epinephrine. * Significantly different from control, $P < 0.05$.

trials. Mean Pes was −6, 1, and −13 cmH_2O during control, unloading, and inspiratory loading, respectively. The Wb during the exercise when no ventilatory intervention occurred varied randomly from trial to trial and averaged 91.6 ± 26.6% of the initial control trial (range 48–188%). Within each subject, V_T, f, minute ventilation ($\dot{V}_E$), arterial P_{CO_2}, pH, P_{O_2}, O_2 saturation, lactate, hemoglobin, and arterial plasma electrolytes (Na^{2+}, K^+, Cl^-) did not change systematically ($P > 0.05$) across the range of Wb values (see Table 2). The ratio of inspiratory time to total time was 0.48 ± 0.22 during unloading, 0.48 ± 0.24 during control, and 0.54 ± 3.2 during loading.

Effects of changing W_b on O_2 transport. Figure 2 shows individual absolute values and each subject's regression for $\dot{Q}$legs, $\dot{V}O_{2legs}$, O_2 extraction, and mean arterial pressure (MAP) vs. Wb. $\dot{Q}$legs and $\dot{V}O_{2legs}$ changed linearly and significantly and at similar slopes with Wb in six out the seven subjects. O_2 extraction averaged 89–91%, and MAP averaged 125.7 ± 2.7 mmHg, neither of which varied across the range of Wb values.

Figure 3 shows the relationship between $\dot{Q}$legs and Wb and between $\dot{V}O_{2legs}$ and Wb across all subjects. Table 3 compares the mean values during control Wb and during unloading and loading. As seen in Fig. 3*A*, during maximal exercise, $\dot{Q}$legs (expressed as %control, across all subjects) showed a significant curvlinear inverse relationship to Wb ($r = -0.84$), with a greater effect occurring during loaded conditions. In absolute terms, during unloading, with a 63% reduction from control in Wb, $\dot{Q}$legs increased an average of 0.8 ± 0.3 l/min ($P = 0.007$), and, with a 28% increase from control in Wb, the decrease in $\dot{Q}$legs averaged 1.3 ± 0.2 l/min ($P = 0.002$) (Table 3). We also emphasize that the effect of the changing Wb on $\dot{Q}$legs was observed even when

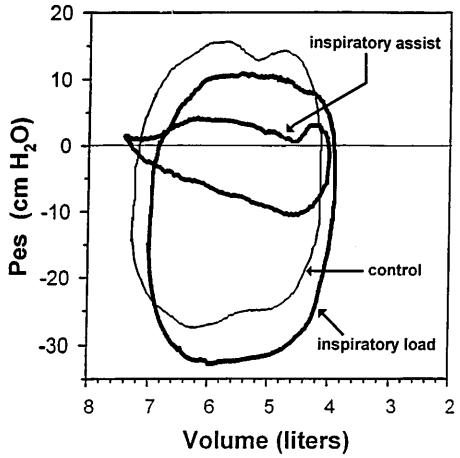

Fig. 1. Pressure-volume loop averaged over 10 breaths from 1 subject at maximal O_2 consumption ($\dot{V}O_{2max}$). Representative loops are from control, inspiratory assist, and inspiratory loaded trials. Pes, esophageal pressure.

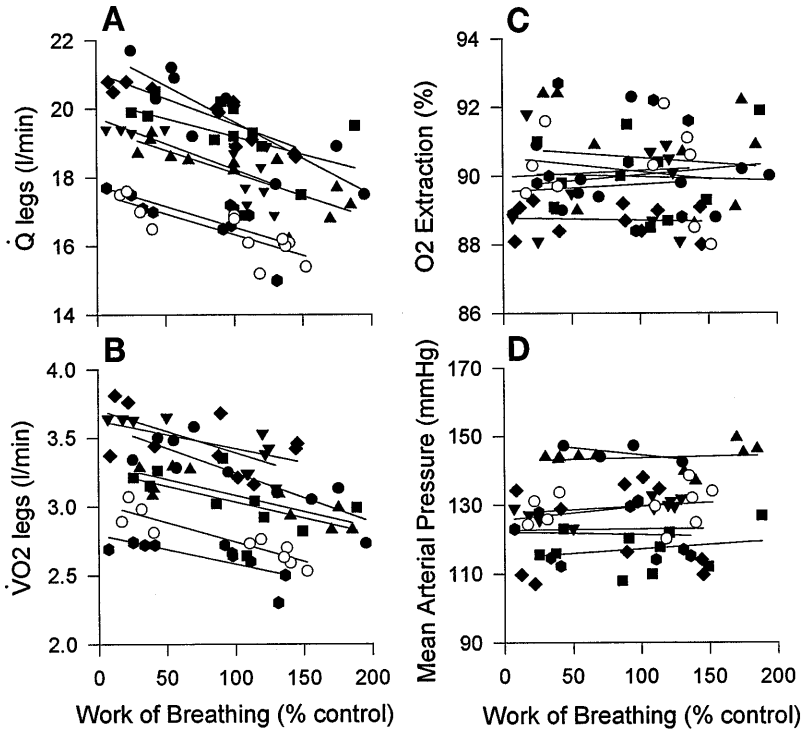

Fig. 2. Absolute values for individual subject plots across range of work of breathing (Wb) values at $\dot{V}O_{2max}$. *A*: leg blood flow ($\dot{Q}$legs) vs. Wb in *subject 1*, $r = -0.60$; *subject 2*, $r = -0.68$; *subject 3*, $r = -0.94$; *subject 4*, $r = -0.92$; *subject 5*, $r = -0.84$; *subject 6*, $r = -0.77$; and *subject 7*, $r = -0.81$. *B*: leg O_2 uptake [$\dot{V}O_2$ ($\dot{V}O_{2legs}$)] vs. Wb in *subject 1*, $r = -0.85$; *subject 2*, $r = -0.57$; *subject 3*, $r = -0.84$; *subject 4*, $r = -0.80$; *subject 5*, $r = -0.78$; *subject 6*, $r = -0.73$; and *subject 7*, $r = -0.91$. *C*: O_2 extraction vs. Wb. There were no significant slopes across Wb. *D*: mean arterial pressure vs. Wb. There were no significant slopes across Wb. Symbols represent individual subjects. Difference between each subject's absolute values for $\dot{Q}$legs and $\dot{V}O_{2legs}$ reflects different absolute maximal exercise loads.

subjects' Wb varied among control trials, showing that artificially altering intrathoracic pressure at maximal work was not required to demonstrate these cardiopulmonary dependencies.

(a-fv)DO_2 and $\%O_2$ extraction at $\dot{V}O_{2max}$ across all trials averaged 18.2 ml/dl and 90.3%, respectively. Figure 3*B* demonstrates that $\dot{V}O_{2legs}$ was inversely related to Wb ($r = -0.77$), and this was due entirely to the change in $\dot{Q}$legs because no change in O_2 extraction occurred (Fig. 2*C*). In absolute terms, with a 67% reduction from control in Wb, $\dot{V}O_{2legs}$ increased an average of 0.10 ± 0.07 l/min ($P < 0.05$) and with a 28% increase from control in Wb, $\dot{V}O_{2legs}$ decreased an average of 0.28 ± 0.06 l/min ($P < 0.05$) (Table 3).

Effects on $\dot{V}O_{2tot}$. Figure 4*A* demonstrates that pulmonary $\dot{V}O_2$ (i.e., $\dot{V}O_{2tot}$) at $\dot{V}O_{2max}$ did not change systematically, as Wb was increased >100% of control. But with ventilatory unloading and reduced Wb, $\dot{V}O_{2tot}$ decreased in most trials, although these effects were highly variable from trial to trial. Also, mean $\dot{V}O_{2tot}$ during all trials with unloading (3.96 ± 0.13) was significantly lower than all trials with loading (4.29 ± 0.11; $P = 0.007$) or control (4.22 ± 0.08; $P = 0.02$) (Table 3).

The significance of a decreased $\dot{V}O_{2tot}$ with inspiratory unloading and unchanged $\dot{V}O_{2tot}$ with inspiratory loading becomes apparent when viewed in relation to the increase in $\dot{V}O_{2legs}$ when Wb was decreased and reduced

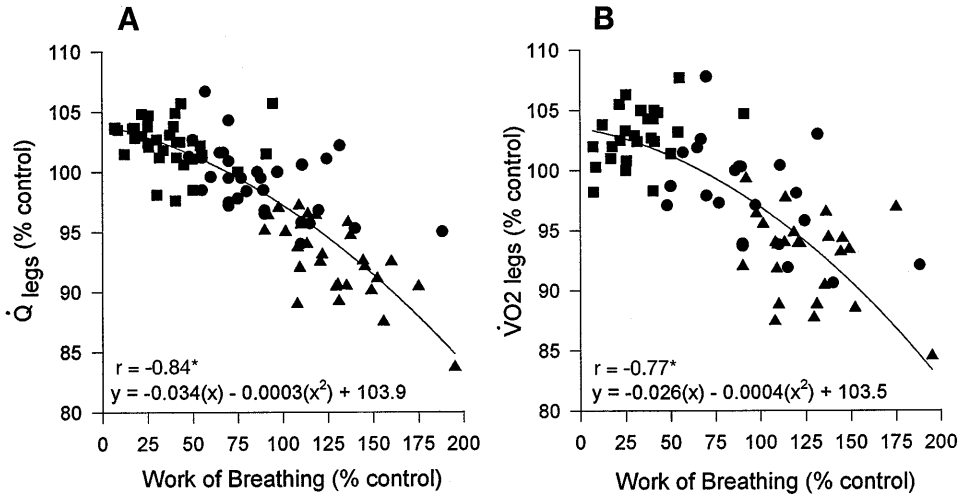

Fig. 3. Relative effects of changing Wb on $\dot{Q}$legs and $\dot{V}O_{2legs}$ for all subjects using all trials. Percent control is calculated from 1st test from each testing session. *A*: $\dot{Q}$legs is significantly related to Wb at $\dot{V}O_{2max}$. *B*: $\dot{V}O_{2legs}$ is significantly related to Wb at $\dot{V}O_{2max}$. The second measurements of blood flow, blood pressure, and blood samples of each test (2:00–2:30 min) were used for interpretation of data. Circles, control; squares, inspiratory unload; triangles, inspiratory load. *Significantly different, $P < 0.05$.

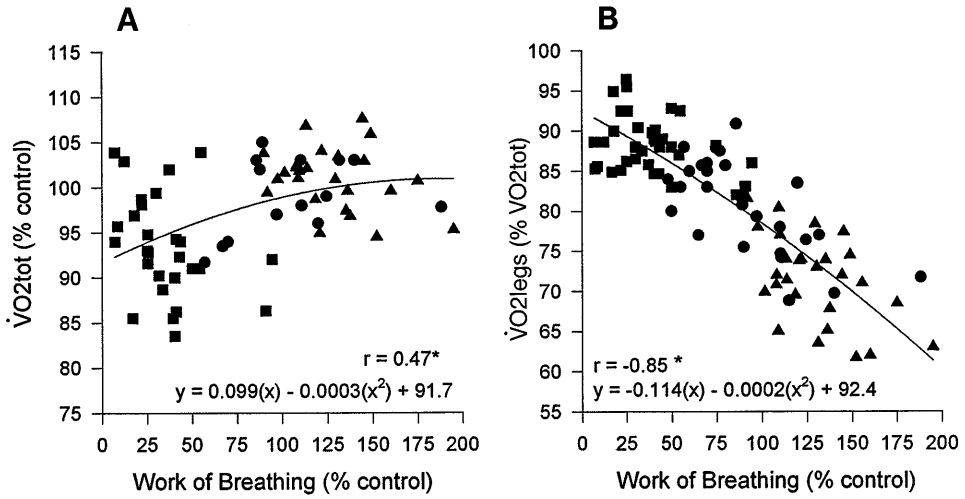

Fig. 4. *A*: total $\dot{V}O_2$ ($\dot{V}O_{2tot}$; respiratory $\dot{V}O_2$) vs. Wb at $\dot{V}O_{2max}$. *B*: $\dot{V}O_{2legs}/\dot{V}O_{2tot}$ vs. Wb at $\dot{V}O_{2max}$. See legend for Fig. 3. *Significantly different, $P < 0.05$.

$\dot{V}O_{2legs}$ when Wb was increased. Figure 4*B* shows the significant relationship of the ratio $\dot{V}O_{2legs}/\dot{V}O_{2tot}$ to Wb. $\dot{V}O_{2legs}$ as a percentage of $\dot{V}O_{2tot}$ was 81 ± 1% during control, 89 ± 1% during trials with unloading ($P = 0.009$), and 71 ± 1% during trials with loading ($P = 0.005$) (see Table 3).

LVR and NE spillover. MAP averaged 125–126 mmHg at $\dot{V}O_{2max}$ under all conditions. Figure 5, *A* and *B*, shows the significant linear positive relationship between LVR and Wb within each individual subject and across all subjects and trials, respectively. Mean values in Table 3 show that with unloading, LVR decreased an average of 7.1 ± 0.5% or 0.5 ± 0.1 mmHg·l^{-1}·min ($P = 0.04$) and with loading, LVR increased an average of 6.2 ± 0.8% or 1.0 ± 0.3 mmHg·l^{-1}·min ($P = 0.001$). Percent changes were similar between LVR and leg vascular conductance.

Figure 5*C* shows the relationship between LVR and NE spillover, and mean values are shown in Table 3. NE spillover was significantly related to LVR ($r = 0.71$). NE spillover increased an average of 78 ± 5% above control with loading, coinciding with a 12.6 ± 3.4% increase in LVR ($P = 0.004$). NE spillover decreased an average of 11 ± 3% below control with unloading and was related to a 1.8 ± 0.4% decrease in LVR ($P = 0.02$).

Effect of transient changes in Wb during constant maximal work rate. Figure 6 shows a representative tracing from one subject of blood pressure, heart rate, and Pes during a 3-min trial at the transitions where

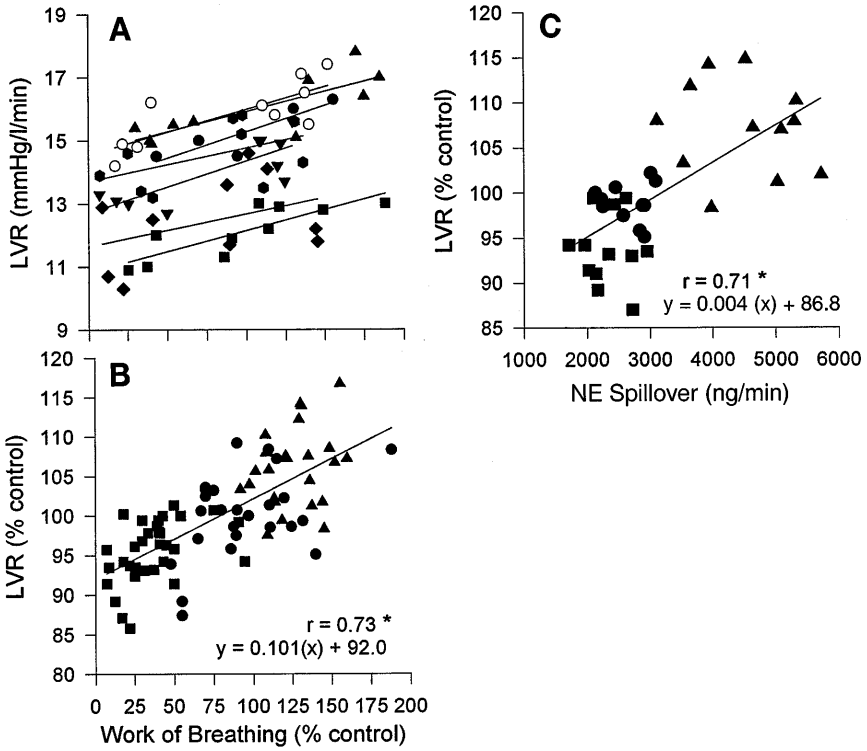

Fig. 5. Leg vascular resistance (LVR). *A*: absolute values for individual subject LVR vs. Wb at $\dot{V}O_{2max}$ for *subject 1*, $r = 0.89$; *subject 2*, $r = 0.83$; *subject 3*, $r = 0.81$; *subject 4*, $r = 0.80$; *subject 5*, $r = 0.69$; *subject 6*, $r = 0.68$; and *subject 7*, $r = 0.78$. *B*: LVR (%control) vs. Wb at $\dot{V}O_{2max}$. As Wb increases, LVR significantly increases. *C*: LVR vs. norepinephrine (NE) spillover at $\dot{V}O_{2max}$. Change in NE spillover is related to change in LVR. See legend for Fig. 3. *Significantly different, $P < 0.05$.

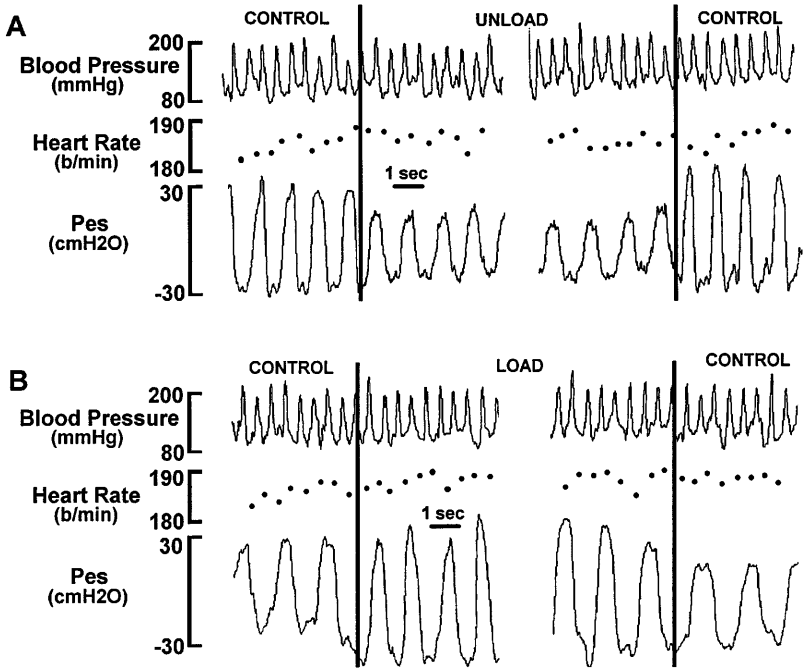

Fig. 6. Representative record from 1 trial of 1 subject at $\dot{V}O_{2max}$ showing blood pressure, heart rate, and esophageal pressure (Pes) transitions during a 3-min trial in which ventilatory conditions were control-inspiratory unload-control (*A*) and control-inspiratory load-control (*B*). Note no change in blood pressure or heart rate despite large changes in Pes.

inspiration was unloaded or loaded within the trial. Systemic arterial blood pressure or heart rate did not change significantly between the transition of the control period to the initiation of inspiratory load or from inspiratory load to control, although Pes changed markedly during these transitions. The 5-beat MAP and heart rate averages for all subjects were 125.6 ± 4.6 mmHg and 184 ± 4 beats/min, respectively, immediately before inspiratory loading ($P > 0.05$) and were 127.2 ± 4.9 mmHg and 185 ± 4 beats/min, respectively, at the onset of inspiratory loading ($P > 0.05$). With inspiratory unloading, the 5-beat MAP averages before and immediately after a decrease in Pes were 126.2 ± 3.9 and 128.1 ± 4.2 mmHg, respectively ($P > 0.05$), whereas systolic and diastolic blood pressure were unchanged. The 5-beat heart rates in these same time periods averaged 185 ± 5 and 184 ± 4 beats/min, respectively ($P > 0.05$).

Mean values for selected variables during the 3-min trials are shown in Table 4. During these continuous tests, a time-dependent effect was present, as noted in the difference in mean values between the first and second control periods of each test. Nevertheless, the changes in Qlegs and $\dot{V}O_{2legs}$ with changing Wb were in a similar direction to those found in a comparison of the intermittent 2.5-min tests with each test conducted at a fixed respiratory load (as reported above). There were no differences in MAP or heart rate between control and loading/unloading conditions during these continuous tests.

DISCUSSION

Summary of findings. Our findings demonstrate a significant effect of the Wb during maximal exercise on locomotor muscle perfusion and $\dot{V}O_2$ in the healthy trained human. We found that changing (increasing and reducing) Wb during maximal exercise caused significant changes in locomotor muscle vascular resistance and perfusion. Significant regressions of $\dot{Q}$legs to Wb were obtained both within individual subjects and across all subjects. The changes in $\dot{Q}$legs were not accompanied by changes in O_2 extraction across the limb; thus $\dot{V}O_{2legs}$ also changed directly with $\dot{Q}$legs and with the Wb. Furthermore, with reduced Wb during maximal exercise, $\dot{V}O_{2tot}$ (respiratory) fell significantly, an effect which, when considered in combination with

Table 4. *MAP, HR, $\dot{Q}$legs, (a-fv)DO_2, $\dot{V}O_{2legs}$, P_I,es_{peak}, and Wb during trials when Wb was changed within trial at $\dot{V}O_{2max}$*

	Control	Unload	Control
	0:30–1:00 min	1:30–2:00 min	2:30–3:00 min
MAP, mmHg	128.5 ± 4.7	131.5 ± 3.5	133.1 ± 3.9
HR, beats/min	186 ± 2	188 ± 2	190 ± 2
$\dot{Q}$legs, l/min	18.0 ± 0.9	18.8 ± 0.8*	18.3 ± 0.4
(a-fv)DO_2, ml/dl	17.9 ± 0.6	18.0 ± 0.5	18.2 ± 0.2
$\dot{V}O_{2legs}$, l/min	3.22 ± 0.10	3.38 ± 0.08*	3.33 ± 0.07
P_I,es_{peak}, cmH_2O	−29.5 ± 0.9	−13.9 ± 0.9*	−31.3 ± 0.8*
Wb, J/min	510.9 ± 17.9	208.9 ± 26.6*	547.2 ± 23.1
	Control	Load	Control
	0:30–1:00 min	1:30–2:00 min	2:30–3:00 min
MAP, mmHg	129.4 ± 5.1	130.9 ± 3.1	131.8 ± 4.1
HR, beats/min	184 ± 2	186 ± 2	189 ± 2
$\dot{Q}$legs, l/min	17.8 ± 1.0	16.9 ± 0.8*	18.1 ± 0.5
(a-fv)DO_2, ml/dl	18.0 ± 0.8	18.0 ± 0.7	18.2 ± 0.3
$\dot{V}O_{2legs}$, l/min	3.20 ± 0.11	3.04 ± 0.10*	3.29 ± 0.04
P_I,es_{peak}, cmH_2O	−27.7 ± 1.1	−34.8 ± 1.1*	−30.8 ± 0.7*
Wb, J/min	517.7 ± 20.3	697.9 ± 39.6*	540.3 ± 20.9

Values are means ± SE; $n = 7$. $\dot{Q}$legs, leg blood flow; P_I,es_{peak}, peak inspiratory esophageal pressure. *Significantly different than 1st control (0:30–1:00), $P < 0.05$.

the corresponding increase in $\dot{V}_{O_{2legs}}$, meant that reducing the normal amount of the work of the respiratory muscles at maximal exercise resulted in a substantial increase in the fraction of $\dot{V}_{O_{2tot}}$ (and presumably total $\dot{Q}$) devoted to working locomotor muscles. Changes in NE spillover across the working limb suggested active, sympathetically mediated alterations in limb vascular resistance triggered by changes in respiratory muscle work, possibly mediated by a respiratory muscle chemoreflex effect. These findings suggest that the level of respiratory muscle work normally engendered during maximal exercise in humans attenuates the rise in $\dot{Q}$ and O_2 transport to working limb locomotor muscles.

Evidence for cardiovascular effects of a changing Wb. The interpretation of our findings is critically dependent on our ability to detect systematic changes in the 1- to 3-liter/min range of limb $\dot{Q}$ during maximal exercise. We believe this degree of sensitivity was achieved through our use of the thermodilution technique and by our experimental design.

The thermodilution technique for the determination of limb $\dot{Q}$ does not have an absolute gold standard for comparison. Thus, criteria for acceptable measurements are based on how stable and reproducible the obtained values are, sensitivity of the technique to be able to detect expected differences, and agreement with the values repeated by others. Accordingly, we found that the $\dot{Q}$legs measurement showed no significant systematic variation within subjects within a maximum WL trial or between trials during maximal exercise. Furthermore, the random variations under these repeat-test conditions were $<\pm 8\%$. In a separate study with one subject, we also found that repeat $\dot{Q}$legs thermodilution measurements were highly sensitive to small ($<10\%$) changes in work rate. These limited observations agree with the sensitivity previously reported by others (17). We also note that our absolute $\dot{Q}$legs values agree with those obtained by others at similar levels of maximal work rate (17, 18, 20, 21).

Equally important, we employed a study design requiring randomly assigned repetitions of maximal work rates under the three conditions of respiratory muscle loading, unloading, and control. These multiple trials allowed us several different means of testing the hypothesis of a significant Wb-$\dot{Q}$legs relationship, that is *1*) within a single subject (at same maximal work rate) as well as across subjects (each at different maximal work rates); and *2*) between maximal work rates conducted intermittently, during which the levels of respiratory muscle loading or unloading were constant throughout the work load, vs. within a maximal work rate, during which loading and unloading were altered during the exercise. These different approaches consistently confirmed a significant association of respiratory muscle work with limb locomotor $\dot{Q}$ at maximal exercise. Furthermore, observed changes in $\dot{Q}$legs and in LVR were indirectly supported by appropriate directional changes in measurements of NE spillover across the working muscle (see Fig. 5).

We presumed that the significant correlations of Wb to $\dot{Q}$legs at constant maximal work rate reflected cause and effect. This interpretation required that our imposition of mechanical unloading (via PAV) or loading (with increased inspiratory resistors) did not exert some additional influences on cardiac output or locomotor muscle vasoreactivity in addition to the postulated effects of changes in intrathoracic pressure and Wb. We noted that V_T and f during maximal exercise remained unchanged with loading and unloading,[1] as did arterial and femoral venous blood gases, acid-base status, and electrolyte concentrations. These findings imply that at least the potential vasomotor effects of pulmonary stretch receptor feedback (26) and several known circulating vasoactive agents (K^+, H^+, P_{O_2}, P_{CO_2}) remained unchanged with respiratory muscle loading and unloading at maximal exercise.

Limitations. For us, a major remaining unknown in quantifying the effects of changes in Wb on local $\dot{Q}$legs is the effect of a changing intrathoracic pressure on total cardiac output. Considerable literature reveals significant but variable effects of changing intrathoracic and ventricular transmural pressures on preload and afterload (and therefore stroke volume) of the healthy heart (19). During maximal exercise, substantial negative and positive intrathoracic pressures occur at peak inspiration (-25 to -30 cmH_2O) and expiration (20 to 25 cmH_2O), respectively. Our unloading and loading protocols had marked effects primarily on inspiratory pressure, and to a lesser extent on expiratory pressure and the difference in pressure from inspiration to expiration (see Table 2; Figs. 1 and 6). Theoretically, a case may be made for either no effect or an enhancing effect of a changing negative intrathoracic pressure and abdominal pressure on stroke volume during exercise. This depends on whether the dominant effect of these pressure changes is on venous return (preload) or on transmural pressure across the myocardium (afterload). Over several breaths, the effect on cardiac output may also depend on changes in the magnitude of pleural pressure differences between inspiration and expiration or the mean pleural pressures. In addition, there may also be significant reflex sympathoexcitatory affects on myocardial contractility and heart rate triggered via feedback from respiratory muscles during respiratory muscle unloading and loading (8, 19).

Our own indirect data on this question of effects of changing intrathoracic pressure on cardiac output are

[1] We do not interpret these unchanged ventilatory responses with loading and unloading to mean that respiratory muscle work has no significant influence on the physiological control of breathing during exercise (6). Rather, it was clear that loading the respiratory muscles with inspiratory resistors and unloading them via PAV at maximal exercise elicited strong and variable behavioral responses to the foreign sensory inputs imposed by these unnatural perturbations. Accordingly, we think that ventilation under these conditions is largely under cortical control, which probably overrides any feedback mechanisms that might be present in response to normally occurring mechanical loads during strenuous exercise.

inconsistent. We observed no immediate transient changes with an increased or decreased inspiratory load (and Pes) on systemic pressures or heart rate (see Fig. 6). This implied to us that left heart stroke volume had also remained unchanged in response to the immediate increases or decreases in intrathoracic pressure. Furthermore, with inspiratory muscle loading, $\dot{V}O_{2tot}$ did not change systematically, also implying that maximal cardiac output had not changed, i.e., the measured reduction in limb $\dot{Q}$ (and $\dot{V}O_{2legs}$) was presumably matched by an equal increase in respiratory muscle $\dot{Q}$ (and $\dot{V}O_2$). However, with respiratory muscle unloading, we did observe a variable yet significant 9.3% (0.39 ± 0.09 l/min) reduction in $\dot{V}O_{2tot}$. If no change occurred in the arterial to mixed venous O_2 content difference with unloading, this reduction in $\dot{V}O_{2tot}$ would mean that cardiac output was also reduced. As explained above, direct measurements of cardiac output are needed to test this proposed effect of unloading.

Another unknown in our study is the actual muscle mass engaged in the exercise. For example, with respiratory muscle loading, $\dot{Q}$legs was reduced and $\dot{V}O_{2legs}$ fell 280 ml/min, and yet the external work rate was maintained for 2.5 min. From what source is the energy expenditure derived to maintain this work rate? An increased lactate metabolism may account for a small portion of this (10), although this was not reflected in changes in circulating lactate concentrations across the working limb (Table 2). A more likely explanation may be to recall that our $\dot{Q}$legs, (a-fv)D_{O_2}, and $\dot{V}O_2$ measurements pertain principally to the quadriceps and hamstring muscles. Accordingly, as $\dot{Q}$ and $\dot{V}O_2$ are reduced in these muscles during respiratory muscle loading, additional "nonfemoral" locomotor muscles such as the gluteus may have been recruited to maintain external power output.

Effects on limb $\dot{Q}$ of changing the mass of working muscle. Although we found that increases in the amount of working respiratory muscle mass significantly reduced limb $\dot{Q}$, most previous studies using arm work added to leg work found no significant effect on limb $\dot{Q}$ (see above). Addition of arm work was shown to increase LVR (21) and to increase NE spillover across the working muscle (20, 21, 25), and this is similar to our findings with added respiratory muscle mass. However, in a study with added arm work, Richter et al. (21) reported that systemic pressure also rose sufficiently to preserve flow to the working limb. The difference in our findings of a reduction in limb flow with added respiratory muscle work is not attributable to the amount of added muscle mass because respiratory and accessory muscles would weigh only about one-third of the estimated 10–15 kg mass of added muscle with arm work (22).

There are two explanations for these disparate findings. First, respiratory muscles may compete more effectively than limb muscles for total $\dot{Q}$ (see below). This possibility is suggested by the increase in diaphragm $\dot{Q}$ and decrease in limb locomotor muscle $\dot{Q}$ during submaximal exercise in rats when Wb was presumably increased via experimental congestive heart failure (14). A second explanation for the apparent discrepancy in findings is the exercise intensity used. That is, the use of submaximal leg exercise intensities in previous studies (see above) meant that substantial reserve was available to increase cardiac output and MAP, and therefore preserve local $\dot{Q}$, whereas during our maximal WL, these reserves were not available when extra working (respiratory) muscle mass was added. A first step toward examining these questions in humans would be to determine the effects of respiratory muscle loading and unloading on locomotor muscle vascular resistance and $\dot{Q}$ at several submaximal exercise intensities.

$\dot{Q}$ redistribution effect—magnitude and mechanism. Our data indicate that respiratory muscles under load competed effectively with limb locomotor muscles for a significant portion of available total cardiac output at maximal exercise. Across the range achieved for respiratory muscle work (7 to 198% of control) at maximal exercise, $\dot{Q}$legs changes averaged 13% or ~2 l/min. Furthermore, changes in $\dot{Q}$legs with changes in Wb were greatest when ventilatory work was increased (rather than decreased) at maximal exercise. This substantial redistribution effect between locomotor and (presumably) respiratory muscles may reflect two important properties of respiratory muscles. The diaphragm and accessory respiratory muscles are of high oxidative capacity; accordingly, their resistance vessels may be especially responsive to local vasodilator influences, as shown in the highly trained limb muscle vasculature (11, 12). Second, increased work by the respiratory muscles has been shown to promote reflex sympathoexcitation and vasoconstriction of systemic vascular beds (8), similar to the reflex pressor responses attributed to type III and IV afferents from contracting limb muscles (Ref. 16; also see below for details). We do not know whether the sensitivity of these vasoactive characteristics are sufficiently different in limb and respiratory muscles to explain the redistribution phenomena we have observed. Finally, a reduced total available cardiac output during unloading (see *Limitations*) may explain in part why the increase in $\dot{Q}$legs during unloading was less than the reduction in $\dot{Q}$legs with loading.

The change in vascular resistance and redistribution of $\dot{Q}$ between respiratory and locomotor muscles as Wb was altered at maximal exercise was accompanied by changes in NE spillover across the working limb muscle. These findings imply an increased muscle sympathetic nerve activity (MSNA) and vasoconstriction with respiratory muscle loading and reduced MSNA and vasodilation with respiratory muscle unloading (25). The vasodilatory effect in response to respiratory unloading is consistent with the concept that a significant level of sympathetically mediated vasoconstriction is normally present in active limb skeletal muscle at maximal exercise (24). Our findings imply further that a significant portion of this vasoconstrictor sympathetic outflow

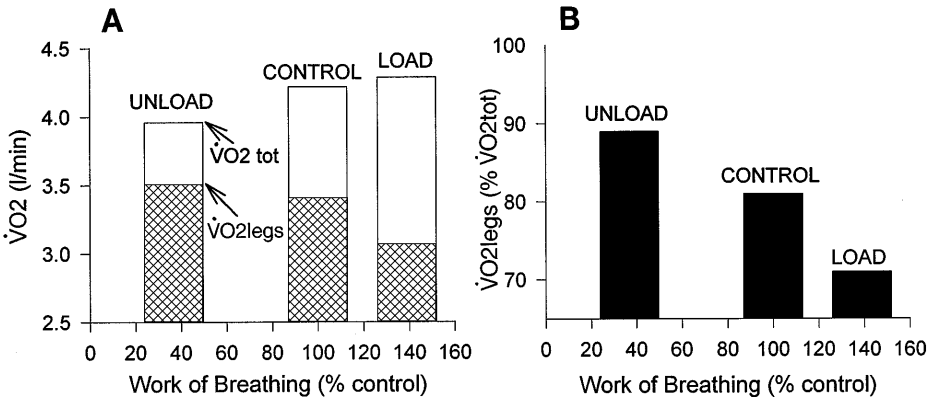

Fig. 7. *A*: $\dot{V}O_{2tot}$ was significantly lower with unloading and unchanged with loading, whereas $\dot{V}O_{2legs}$ was significantly increased with unloading and decreased with loading. *B*: respiratory muscle unloading increased and respiratory muscle loading reduced the fraction of total O_2 consumed by the legs.

during maximal exercise may emanate from tonically active respiratory muscle chemoreflexes (see below).

Two reflexes might be invoked to explain the changes in sympathetic outflow. First, arterial baroreceptor stimulation may have triggered reflex sympathetic excitation/withdrawal as changes in Wb caused changes in respiratory muscle perfusion. However, the role of baroreceptor feedback effects on sympathetic efferent activity is difficult to evaluate in these complex conditions of large dynamic changes in intrathoracic pressure during maximal exercise: *1*) we did not observe even transient changes in systemic blood pressure with loading or unloading (see Fig. 6); however, aortic arch baroreceptor tissue might undergo deformation even in the absence of changing blood pressure, as shown during lower body negative pressure at rest (28); *2*) ventricular mechanoreceptors sensitive to cardiac filling pressures would be influenced by any changes in venous return; and *3*) aortic baroreceptors are also affected "directly" by changes in intrathoracic, and therefore in aortic, transmural pressures (3). The predicted changes in cardiac filling pressure or aortic transmural pressure with respiratory muscle loading/unloading would be in the opposite direction expected to elicit the observed reflex vasoconstriction/vasodilation in limb locomotor muscle. Furthermore, our findings that transient changes in heart rate did not occur with unloading/loading are also indicative that systemic baroreceptors were not influenced by the respiratory changes. A more likely candidate for mediation of reflex vasoconstriction is the muscle chemoreflex, a sensitive feedback mechanism known to originate from type III and IV afferents in contracting limb muscles (24) and in the diaphragm (8). On stimulation of their thin-fiber phrenic afferent pathways in the diaphragm, sympathoexcitation and vasoconstriction in both respiratory and resting limb skeletal muscle can be induced (8).

Effects of Wb on distribution of total maximal O_2 transport. The effects of partial respiratory muscle unloading on increasing limb muscle $\dot{Q}$ speak directly to the question of the physiological relevance of Wb normally achieved during maximal exercise to O_2 transport to locomotor muscles. It is not unexpected that the respiratory muscle work normally achieved in maximal exercise would require a significant share of maximal cardiac output. In humans, indirect estimates of the O_2 cost of maximal exercise hyperpnea are as high as 15% of $\dot{V}O_{2tot}$ in highly fit subjects who achieve significant expiratory flow limitation in heavy exercise and 8 to 12% in the normally fit who undergo little or no airflow limitation at maximal exercise (1). Most of our fit subjects in the present study would have been grouped with those with the higher O_2 cost of breathing, although we would also expect to see significant but smaller effects of unloading on $\dot{Q}$legs in less fit subjects at lower maximal work loads and with little or no expiratory flow limitation.

Our findings from unloading the respiratory muscles also showed that the Wb normally achieved at maximal exercise has a significant effect on leg locomotor muscle $\dot{V}O_2$. At maximal exercise, reducing (or increasing) Wb had no effect on O_2 extraction across the leg locomotor muscles, which was probably at its maximum capacity; thus, as $\dot{Q}$legs increased, locomotor muscle $\dot{V}O_2$ also increased. Along with this increase in $\dot{V}O_{2legs}$, respiratory muscle unloading also reduced $\dot{V}O_{2tot}$. Accordingly, $\dot{V}O_{2legs}$, as a fraction of $\dot{V}O_{2tot}$, increased markedly with respiratory muscle unloading (see Fig. 7), showing that the effect of respiratory muscle work on $\dot{V}O_{2legs}$ is even more substantial in terms of redistributing the "available" total O_2 transport. The reduced $\dot{V}O_{2tot}$ also indicates that with unloading, all O_2 uptake "released" by the respiratory muscles was not manifested in $\dot{V}O_{2legs}$; however, as discussed earlier, we are unable to evaluate the cause of this reduced $\dot{V}O_{2tot}$ until we know the coincident effects on cardiac output.

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