Threshold effects of respiratory muscle work on limb vascular resistance

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Received 7 September 2001; accepted in final form 3 December 2001

Sheel, A. William, P. Alexander Derchak, David F. Pigelelow, and Jerome A. Dempsey. Threshold effects of respiratory muscle work on limb vascular resistance. Am J Physiol Heart Circ Physiol 282: H1732–H1738, 2002; 10.1152/ajpheart.00798.2001.—The purpose of this study was to determine whether the human diaphragm, like limb muscle, has a threshold of force output at which a metaboreflex is activated causing systemic vasoconstriction. We used Doppler ultrasound techniques to quantify leg blood flow (QL) and utilized the changes in mouth twitch pressure (ΔPMT) in response to bilateral phrenic nerve stimulation to quantify the onset of diaphragm fatigue. Six healthy male subjects performed four randomly assigned trials of identical duration (8 ± 2 min) and breathing pattern [20 breaths/min and time spent on inspiration during the duty cycle (time spent on inspiration/total time of one breathing cycle) was 0.4] during which they inspired primarily with the diaphragm. For trials 1-3, inspiratory resistance and effort was gradually increased [30, 40, and 50% maximal inspiratory pressure (MIP)], diaphragm fatigue did not occur, and QL, limb vascular resistance (LVR), and mean arterial pressure remained unchanged from control (P > 0.05). The fourth trial utilized the same breathing pattern with 60% MIP and caused diaphragm fatigue, as shown by a 30 ± 12% reduction in PMT with bilateral phrenic nerve stimulation. During the fatigue trial, QL, and LVR were unchanged from baseline at minute 1, but LVR rose 36% and QL fell 25% at minute 2 and by 52% and 30%, respectively, during the final minutes of the trial. Both LVR and QL returned to control within 30 s of recovery. In summary, voluntary increases in inspiratory muscle effort, in the absence of fatigue, had no effect on LVR and QL, whereas fatiguing the diaphragm elicited time-dependent increases in LVR and decreases in QL. We attribute the limb vasoconstriction to a metaboreflex originating in the diaphragm, which reaches its threshold for activation during fatiguing contractions.

diaphragm fatigue; leg blood flow; metaboreflex threshold; Doppler ultrasound; bilateral phrenic nerve stimulation

IT IS WELL ESTABLISHED THAT thinly myelinated group III and unmyelinated IV afferent nerve fibers innervate limb skeletal muscle. These afferents are stimulated by metabolic byproducts (23), mechanical deformation (29), temperature (18), and vascular distension during muscular contraction (4). Stimulation of these afferents during muscular contraction elicits a powerful pressor response where sympathetic vasoconstrictor outflow is augmented to both resting and exercising skeletal muscle. A threshold exists for activation of this metaboreflex as numerous human studies have demonstrated a link between the metabolic events occurring within a contracting muscle (forearm) and the cardiovascular adjustments to handgrip exercise (3, 21). The current concept is that inadequate blood flow (or O2 delivery) to the contracting muscle leads to an increase in the concentration of metabolites and the stimulation of chemosensitive afferents (type IV). The resulting cardiovascular adjustments (increased heart rate, blood pressure, cardiac contractility, cardiac output, and reflex vasoconstriction of inactive vascular tissue) are thought to enhance blood flow to the active muscle and reduce the error between metabolism and blood flow (19).

As a skeletal muscle, the diaphragm is also innervated by group III and IV afferent nerve fibers (2), and evidence has begun to accumulate that points to stimulation of these receptors during fatiguing contractions with subsequent activation of sympathetic outflow. First, an increase in firing rate of chemosensitive type IV afferent fibers in the diaphragm was observed in the anesthetized rat commissure with the development of diaphragm fatigue secondary to phrenic nerve electrical stimulation (7). Second, electrical stimulation of phrenic afferent fibers evoked sympathoexcitatory responses in anesthetized animals (14, 26) and chemical stimulation resulted in vasoconstriction in selected vascular beds (9). Third, in humans, we have demonstrated that an increase in muscle sympathetic nerve activity (MSNA) in the resting limb occurs over time in response to repeated diaphragm contractions, as induced by voluntary inspiratory efforts against resistance with a prolonged duty cycle taken to the point of task failure (24). Finally, we (22) recently observed a time-dependent decrease in blood flow to the resting limb (QL) and increase in leg vascular resistance (LVR) when fatiguing levels of inspiratory muscle force were

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H1732
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generated. So, a reflex, which causes a sympathetically mediated vasoconstriction, appeared to occur in the contracting diaphragm. Whereas it is known that a threshold exists for metaboreflex activation during forearm contractions (3, 21), it is not known whether the same threshold for activation occurs within the contracting diaphragm.

We sought to determine whether the human diaphragm, like limb skeletal muscle, had a threshold of force output or central motor command, to activate this reflex and its cardiovascular sequelae or whether this threshold required fatiguing contractions. To this end, we used Doppler ultrasound techniques to measure femoral artery blood velocity and vessel diameter because the intensity of force output of the diaphragm was progressively increased via voluntary efforts. We also used phrenic nerve stimulation to quantify the onset of diaphragm fatigue while the intensity of diaphragm contractions were progressively increased.

MATERIALS AND METHODS

General procedures. After the testing procedures were explained verbally, written informed consent was obtained from all subjects. Healthy male volunteers (n = 6, age range of 25–36 yr) served as subjects and were normotensive and free from cardiovascular, neurological, and pulmonary disease. The Health Sciences Human Subjects Committee of the University of Wisconsin-Madison approved all experimental procedures and protocols. For all trials, subjects were studied in a semirecumbent position. Subjects breathed through a mouthpiece with the nose occluded. Airflow rates, tidal volume (VT), mouth pressure (P<sub>OM</sub>), and end-tidal P<sub>CO<sub>2</sub></sub> were measured using equipment and techniques described previously (24, 33). Inspiratory muscle force development was calculated as the product of the time integral of P<sub>M</sub> (F<sub>M</sub>) and breathing frequency (f<sub>0</sub>). Ribcage and abdominal excursions were monitored using a direct-current-coupled respiratory inductive plethysmograph (Respitrace, Ambulatory Monitoring; Ardsley, NY). End-tidal P<sub>CO<sub>2</sub></sub> was maintained at eucapnic levels throughout all experiments by adding CO<sub>2</sub> as necessary to the inspiratory circuit. Because the intensity of force output of the diaphragm was progressively increased via voluntary efforts, subjects were instructed to maintain a square wave in PM throughout each inspiration and isolate respiratory inductive plethysmograph (Respitrace, Ambulatory Monitoring; Ardsley, NY). The point where three consecutive breaths failed to reach the set PM level was defined as the onset of diaphragm fatigue. Compliance with these instructions was monitored with a preset target for each inspiration. Throughout this trial, the subjects maintained an f<sub>0</sub> of 20 breaths/min and a duty cycle T<sub>i</sub>/T<sub>tot</sub> (where T<sub>i</sub> is the time spent on inspiration and T<sub>tot</sub> is the total duty time of one breathing cycle) of 0.4 by listening to a computer-generated audio signal with distinct inspiratory and expiratory tones. End-tidal P<sub>CO<sub>2</sub></sub> was maintained within ±2 mmHg of eucapnic baseline levels. During each inspiratory effort, subjects were instructed to maintain a steady wave in P<sub>M</sub> throughout each inspiration and isolate the diaphragm. Compliance with these instructions was monitored with inspection of P<sub>M</sub> measurements and abdominal excursions of the respiratory inductive plethysmograph. At the point where three consecutive breaths failed to reach the target P<sub>M</sub> subjects were instructed to continue to attempt to reach the target for one additional minute.

As a result of completing several preliminary trials at different intensities of P<sub>M</sub>, the subjects experienced task failure and fatigue after 3–8 min at the 60 ± 10% MIP work rate. Accordingly, the subjects then completed the 60% MIP intensity fatiguing trial to task failure, and measures of MAP, Q<sub>L</sub>, LVR, and respiratory variables were made throughout. On subsequent days, subjects completed the 30, 40, and 50% MIP trials in random order for the identical length of time they each completed for the fatiguing trial.

Statistical analyses. Measurements of PaTP elicited by phrenic nerve stimulation before and after fatiguing diaphragm contractions were compared using Student’s paired t-tests. Mean 1-min values for respiratory variables, heart rate, blood pressure, and blood flow measured during each of the trials were compared across time using a two-way, repeated-measures ANOVA (protocol × time). When significant F ratios were detected, Tukey’s significant-difference tests were applied post hoc to ascertain where the differences resided. For all procedures, statistical significance was set at P < 0.05. Values are presented as means ± SD.

Ultrasound Doppler measurements. An ultrasound Doppler system (Image Point Hx, Hewlett-Packard; Andover, MA) equipped with a transducer probe (model L1038) operating at an imaging frequency of 7.5 MHz and variable Doppler frequencies of 4.0–7.5 MHz was utilized to simultaneously measure two-dimensional femoral artery diameter and blood velocity. All measurements were performed with the transducer probe positioned over the common femoral artery 2–3 cm distal to the inguinal ligament. Beat-by-beat blood velocity was calculated as the integrated area [velocity time integral (VTI)] by integrating the total area under the outer envelope of the maximal velocity values of the blood velocity profile over the R-R interval of the electrocardiogram tracing. The cross-sectional area of the femoral artery (A<sub>FA</sub>) was determined by positioning on-screen callipers at 1-min intervals during each trial. We did not observe any significant variation in femoral artery diameter during any of the experimental protocols. Q<sub>L</sub> was calculated similar to previously published methods (10, 16, 22) as

\[ Q_L (\text{ml/min}) = A_{FA} (\text{cm}^2) \cdot \text{VTI (cm/beat)} \]
RESULTS

Measurement of blood flow and arterial diameter. Our values for resting QL (−0.4 l/min) are in close agreement with other studies (10, 16) that have calculated blood velocity using integration of the outer envelope of the maximal velocity values in the flow profile. The mean within-subject coefficient of variation for repeated measures under control conditions (rest and eupnea) was ±6.1% for Qtot, which was also in close agreement with reported values (±7.2%) (17). Femoral arterial diameter obtained during control ranged among subjects from 0.65 to 0.96 cm. Within each of the six subjects during control conditions, there was an average coefficient of variation of ±1.6%. None of the subjects showed a significant change in vessel diameter during any of the protocols of increasing diaphragmatic work (P > 0.05).

Evaluation of diaphragm fatigue. Figure 1 shows the relationship between PMT and lung volume, expressed as percentage of inspiratory capacity, in one representative subject during conditions of control (rest) and after breathing at 50% and 60% MIP with a T/Ttot = 0.4 and f50 = 20 breaths/min for 7 min, 15 s. After the 60% MIP trial, the relationship was shifted upward (PMT intercept = −8.3 cmH2O) compared with control (PMT intercept = −11.8 cmH2O) indicating reduced force output at all lung volumes (and presumably diaphragm lengths) in response to supramaximal BPNS. After the 50% MIP trial the PMT intercept (−12.4 cmH2O) was not changed from the control value.

For the group, the 60% MIP trial produced significant fatigue, as noted by a significant reduction in the PMT intercept to 70 ± 12% of control at task failure (P < 0.05) whereas the 50% MIP trial produced no significant change (PMT intercept = 97 ± 8% of control) (P > 0.05). The presence or absence of fatigue was confirmed by single 1-Hz BPNS stimulation at functional residual capacity, which also showed a significant reduction in PMT (−25 ± 14%) after trials at 60% MIP (P < 0.05) and no significant change after trials at 50% MIP (P > 0.05). Subjects performed each protocol for 485 ± 154 s (range of 3−9 min), which was the time taken for each subject to achieve task failure at the highest intensity of MIP.

Cardiovascular effects of progressive increases in inspiratory effort. During all trials, none of the subjects performed inadvertent leg contractions as evidenced by the lack of EMG activity from the quadriceps muscle. Figure 2 shows beat-by-beat Doppler data for one representative subject breathing at trials of increasing inspiratory effort. VTI values were unchanged during the 30, 40, and 50% MIP trials. During the 60% MIP trial, VTI values were variable during the first minute, decreased to a nadir by the second minute, and remained at this level for the remainder of the trial. In this subject, MAP was unchanged during the 30, 40, and 50% MIP trials and was elevated +9 mmHg during the final min of the 60% MIP trial. On cessation of the experimental breathing maneuvers, VTI values rapidly returned to control values (<30 s).

Figure 3 and Table 1 show group mean values for each of the trials. During each successive trial of increasing PM, JPM × f50 increased significantly compared with control (119, 152, 196, and 205 times eupnea levels, respectively). Mean heart rate increased significantly (+9 to 15 beats/min) in all trials during the first minute and stayed elevated throughout. MAP did not change significantly during any of the trials (P > 0.05), although there was a trend for MAP to increase (+3 ± 8 mmHg, range = 0 to 18) during the final min of the 60% MIP trial (P > 0.05). QL and LVR were unchanged throughout each of the 30, 40, and 50% MIP trials (P > 0.05). During the fatiguing 60% MIP trial, QL and LVR were unchanged from eupneic control in the initial minute of increased inspiratory effort, but thereafter fell gradually over time and by the final minute of the trial, QL was reduced by 30 ± 13% and LVR increased 52 ± 24% compared with control (P < 0.05). This was a consistent observation whereby all subjects demonstrated a reduction in QL (range = −15 to 48%) and an increase in LVR (range = +23 to 94%).

DISCUSSION

When high levels of inspiratory muscle force were rhythmically generated we observed a time-dependent decrease in blood flow to the resting limb and an increase in leg vascular resistance, which coincided with the onset of diaphragm fatigue. We observed no change in blood flow or leg vascular resistance during three levels of progressive increases in force output of the diaphragm, which did not result in diaphragm fatigue. We conclude that sympathetically mediated vasoconstriction in the resting limb was elicited by a metaboreflex originating in the diaphragm, which reached its threshold for activation during fatiguing contractions. The increase in limb vascular resistance observed during fatiguing diaphragm work is similar to the threshold observed during increasing intensities of handgrip exercise (20, 21).
Fig. 2. Beat-by-beat Doppler data in velocity time integral (VTI) from one representative subject during eupnea, breathing at 30% (A), 40% (B), 50% (C), and 60% (D) MIP with a $T_i/T_{tot} = 0.4$ and $f_b = 20$ breaths/min and during recovery. Significant diaphragm fatigue was observed via bilateral phrenic nerve stimulation (BPNS) in this subject only during the 60% MIP trial. Limb vascular resistance changes (% control) during the final minutes were -1%, +10%, +15%, and +61% for 30%, 40%, 50%, and 60% MIP trials, respectively.

Fig. 3. Mean values for arterial blood pressure (MAP), leg blood flow (QL), limb vascular resistance (LVR), tidal volume ($V_T$), the product of integrated mouth pressure ($P_{M} \times f_b$), and mean inspiratory flow rate ($V_{M}/T_i$) during protocols of increasing inspiratory effort while breathing at $T_i/T_{tot} = 0.4$ and $f_b = 20$ breaths/min. The final minute ("end") of the trial occurred with task failure, after 485 ± 154 s (range 3–9 min). Only the trials at 60% MIP showed a significant diaphragm fatigue (see Fig. 1). Statistical symbols omitted for clarity. 60% MIP values for QL and LVR statistically different from control at minute 2 and end. $V_T$ was statistically different from control at minute 1, minute 2, and end for the 30, 40, and 50% MIP trials. $P_{M} \times f_b$ and HR were statistically different from control at minute 1, minute 2, and end for all trials. $P < 0.05$, for all statistical comparisons ($n = 6$).
Table 1. Group mean data for protocols of increasing inspiratory muscle force output

<table>
<thead>
<tr>
<th>Protocol</th>
<th>(Q_L), l/min</th>
<th>MAP, mmHg</th>
<th>LVR, mmHg·m⁻¹·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% MIP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eupnea</td>
<td>0.402 ± 0.099</td>
<td>86.2 ± 8.5</td>
<td>0.230 ± 0.079</td>
</tr>
<tr>
<td>Minute 1</td>
<td>0.393 ± 0.123</td>
<td>81.8 ± 9.2</td>
<td>0.227 ± 0.078</td>
</tr>
<tr>
<td>End</td>
<td>0.386 ± 0.127</td>
<td>85.7 ± 7.8</td>
<td>0.256 ± 0.133</td>
</tr>
<tr>
<td>40% MIP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eupnea</td>
<td>0.390 ± 0.105</td>
<td>88.7 ± 7.7</td>
<td>0.244 ± 0.078</td>
</tr>
<tr>
<td>Minute 1</td>
<td>0.389 ± 0.117</td>
<td>81.8 ± 13.1</td>
<td>0.228 ± 0.073</td>
</tr>
<tr>
<td>End</td>
<td>0.355 ± 0.091</td>
<td>87.2 ± 9.9</td>
<td>0.260 ± 0.126</td>
</tr>
<tr>
<td>50% MIP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eupnea</td>
<td>0.395 ± 0.112</td>
<td>84.2 ± 5.7</td>
<td>0.240 ± 0.092</td>
</tr>
<tr>
<td>Minute 1</td>
<td>0.390 ± 0.124</td>
<td>81.4 ± 5.9</td>
<td>0.235 ± 0.105</td>
</tr>
<tr>
<td>End</td>
<td>0.360 ± 0.127</td>
<td>86.9 ± 7.6</td>
<td>0.274 ± 0.134</td>
</tr>
<tr>
<td>60% MIP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eupnea</td>
<td>0.441 ± 0.189</td>
<td>87.9 ± 8.4</td>
<td>0.238 ± 0.115</td>
</tr>
<tr>
<td>Minute 1</td>
<td>0.360 ± 0.131</td>
<td>88.1 ± 10.6</td>
<td>0.276 ± 0.108</td>
</tr>
<tr>
<td>End</td>
<td>0.300 ± 0.141*</td>
<td>91.3 ± 10.3</td>
<td>0.381 ± 0.213*</td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n\), 6 males \(Q_L\), leg blood flow; MAP, mean arterial pressure; LVR, limb vascular resistance; MIP, maximal inspiratory pressure; \(f_b\), breathing frequency. All trials were conducted at \(f_b = 20\) breaths/min and \(T/T_{TOT} = 0.4\), where \(T/T_{TOT}\) refers to the time spent on inspiration and one breathing cycle in a duty cycle. End time for all protocols = 485 ± 154 s. *\(P < 0.05\), significantly different from eupnea.

Respiratory muscle metaboreflex threshold. Alam and Smirk (1) were the first to suggest that metabolites within exercising limb muscle stimulate sensory nerves, thus evoking an exercise pressor response. More recently, metaboreflex effects on MSNA or leg vascular resistance from the static or rhythmic contractions of the forearm have been distinguished from the effects of central command through the use of postexercise vascular occlusion as an experimental paradigm (21). Most studies in rhythmically contracting skeletal muscle in humans (29) or animals (15) show that the cardiovascular effects of the limb muscle metaboreflex are not manifested until high-intensity exercise is performed (21) and/or muscle blood flow is markedly reduced (15). Similarly, in the present study, we demonstrated that rhythmic diaphragm contractions leading to fatigue reduced \(Q_L\) and increased LVR; but that nonfatiguing contractions performed for the identical length of time had no effect on vascular resistance.

The reduction in \(Q_L\) and increase in LVR we observed during fatiguing contractions of the diaphragm appear to be due primarily to a sympathetically mediated metaboreflex arising from a fatiguing diaphragm. This is supported by several observations. First, the changes in \(Q_L\) and LVR coincide with the time-dependent increases in muscle sympathetic nerve activity in the resting leg previously found during high levels of inspiratory muscle work sufficient to cause task failure (24). Second, the time course of changes in \(Q_L\) and LVR are consistent with a buildup of muscle metabolites (12). Third, the diaphragm has an abundance of type IV metaboreceptors (2), and in anesthetized rats, fatiguing the diaphragm via phrenic nerve stimulation caused a twofold, time-dependent increase in type IV afferent discharge (14).

We use the term “fatiguing contractions” of the diaphragm to define conditions under which limb vasconstriction was initiated, because we used the BPNS test to define whether diaphragm fatigue was or was not present. Nonetheless, it is certainly conceivable that metabolic end products may be accumulating in the diaphragm, which were sufficient to stimulate type IV receptors but insufficient to cause measurable reductions in muscle force output in response to supramaximal BPNS. For example, in some instances, near-maximum levels of rhythmic diaphragm force output were sustained for several minutes, and MSNA (24) or limb vascular resistance (22) increased significantly in the final minute, although no diaphragm fatigue was detectable via BPNS. So, in lieu of a more sensitive index of these metabolic changes in the diaphragm (as is available, for example, via NMR imaging in limb muscle (28)), our prediction that the metaboreflex “threshold” occurs coincident with the onset of diaphragm fatigue must be considered as a conservative estimate of the minimum amount of rhythmic work required by the diaphragm to elicit a metaboreflex effect on limb vascular resistance.

Large inspiratory efforts will augment intra-abdominal pressure and cause more negative intrathoracic pressures, both of which might elicit transient mechanical or reflex effects on limb vascular resistance (32). However, large inspiratory efforts, by themselves, were without effect on \(Q_L\), LVR, or MSNA as shown at the onset of the 60% MIP protocol (see Fig. 3) or when carried out briefly and without fatigue at near-maximal inspiratory efforts and \(P_M\) (22, 24).

Locomotor versus respiratory system influences on muscle vasconstriction. The locomotor and respiratory system control of sympathetic vasoconstrictor outflow to skeletal muscle in the intact human is similar with respect to the metaboreflex threshold effects but quite dissimilar in terms of the effects of central command. First, rhythmic or static forearm exercise at intensities below 70–75% of maximum causes increases in MSNA and limb vasconstriction only in a time-dependent fashion as fatigue develops and presumably muscle metabolites accumulate (30). Fatiguing contractions of the diaphragm produced a very similar time-dependent response (see Fig. 3). Second, the effects of high levels of central command to locomotor muscles have also clearly been shown to have a threshold of force output and effort, at which MSNA and muscle vasconstriction are activated in the absence of muscle fatigue (30). However, this threshold for increasing limb MSNA or LVR is not apparent in the case of increases in central inspiratory motor output per se, even up to almost maximum levels of inspiratory muscle force output (22, 24). This lack of effect of increased central inspiratory motor output held for both time-course changes in LVR (see Fig. 3) and MSNA, and within-breath changes in MSNA (22, 24, 25). These negative findings concerning activation of sympathetic vasconstrictor via central respiratory motor output,
contrast sharply with the highly significant effects of even relatively small changes in inspiratory effort on parasympathetically mediated increases in heart rate (see Fig. 3) and in the magnitude of respiratory sinus arrhythmia (25).

The reasons that the intact human does not show an apparent threshold effect on MSNA or limb vascular conductance in response to increases in central respiratory motor output may be because of very strong inhibitory feedback effects, which accompany inspiration, especially when VT (or functional residual capacity) is elevated and systemic BP tends to rise during inspiration (22, 25). The considerable strength of these inhibitory feedback influences on MSNA and LVR associated with lung inflation has been previously documented (22, 25).

There are instances in the intact animal or human where an increased “drive” to breathe does indeed coincide with increased MSNA (8). For example, chemoreceptor stimulation in humans via hypoxia and/or CO₂ markedly increases MSNA in a dose-dependent manner, even in the face of increased VT and minute ventilation (13). However, other studies (8, 25, 27) during apnea in humans and in anesthetized cats show that sympathetic responses to carotid body stimulation occur via pathways, which are independent of the central respiratory pattern generator and of respiratory motor output. In our present studies, we used cortically driven voluntary efforts to increase inspiratory motor output and this volitional increase in the drive to breathe, unlike chemoreceptor stimulation, had no effect on sympathetic outflow in the face of increased ventilation. Whether other nonchemoreceptor inputs to respiratory motor output, such as inputs that occur during exercise, will independently influence sympathetic outflow remains to be determined.

In conclusion, we attribute the observed changes in Q₁ and LVR to a metaboreflex originating in the diaphragm, which, like that in limb muscle, reaches its threshold for activation during fatigue-inducing contractions. On the basis of these findings, we predict that diaphragm fatigue will elicit sympathetically mediated vasoconstriction in resting limb muscle and perhaps also in other vascular beds, such as the coronary and renal circulation, which have been shown in anesthetized animals to increase their sympathetic nerve activity in response to electrical or pharmacological stimulation of phrenic nerve afferents (9, 14, 26).

Under what real-life circumstances might this diaphragm metaboreflex be activated? During heavy sustained exercise in healthy humans, diaphragmatic fatigue occurs (11) and the use of mechanical ventilation to reduce ventilatory work causes a reduced norepinephrine spillover, vasodilation, and increased blood flow to the exercising limb and an increase in exercise performance (5, 6). However, if exercise intensity was submaximal (<80% V₀₂ max), diaphragm fatigue did not occur (11), and mechanically unloading the respiratory muscles at these lower exercise intensities did not affect limb vascular resistance or blood flow to the exercising leg (31). This difference in the cardiovascular effects of respiratory muscle unloading between moderate and heavy intensity whole body exercise may be explained by present findings, which show that the threshold for the respiratory muscle metaboreflex is exceeded only when muscular efforts resulted in fatigue. Confirmation of this postulate requires further study to determine whether our respiratory muscle metaboreflex, by itself, does indeed, cause significant vasoconstriction in locomotor muscles during whole body exercise.

This work was supported by National Heart, Lung, and Blood Institute Grant HL-15469 and a training grant to P. A. Derchak (T32HL-07654).

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