Augmented sympathetic tone alters muscle metabolism with exercise: lack of evidence for functional sympatholysis

J. KEVIN SHOEMAKER,1 PRASANT PANDEY,1 MICHAEL D. HERR,1 DAVID H. SILBER,1 QING X. YANG,1 MICHAEL B. SMITH,1 KRISTEN GRAY,2,1 AND LAWRENCE I. SINOWAY1,2

1Division of Cardiology, The Milton S. Hershey Medical Center, Hershey 17033; and 2Lebanon Veterans Affairs Medical Center, Lebanon, Pennsylvania 17042

Shoemaker, J. Kevin, Prasant Pandey, Michael D. Herr, David H. Silber, Qing X. Yang, Michael B. Smith, Kristen Gray, and Lawrence I. Sinoway. Augmented sympathetic tone alters muscle metabolism with exercise: lack of evidence for functional sympatholysis. J. Appl. Physiol. 82(6): 1932–1938, 1997.—It is unclear whether sympathetic tone opposes dilator influences in exercising skeletal muscle. We examined high levels of sympathetic tone, evoked by lower body negative pressure (LBNP, −60 mmHg) on intramuscular pH and phosphocreatine (PCr) levels [31P-nuclear magnetic resonance spectroscopy] during graded rhythmic handgrip (30 contractions/min; ~17, 34, 52 and 69% maximal voluntary contraction). Exercise was performed with LBNP and without LBNP (Control). At the end of exercise, LBNP caused lower levels of muscle pH (6.59 ± 0.09) compared with Control (6.78 ± 0.05; P < 0.05). PCr recovery, an index of mitochondrial respiration, was less during the recovery phase of the LBNP trial. Exercise mean arterial pressure was not altered by LBNP. The protocols were repeated with measurements of forearm blood flow velocity and deep venous samples (active forearm) of hemoglobin (Hb) saturation, pH, and lactate. With LBNP, mean blood velocity was reduced at rest, during exercise, and during recovery compared with Control (P < 0.05). Also, venous Hb saturation and pH levels during exercise and recovery were lower with LBNP and lactate was higher compared with Control (P < 0.05). We conclude that LBNP enhanced sympathetic tone and reduced oxygen transport. At high workloads, there was a greater reliance on nonoxidative metabolism. In other words, sympatholysis did not occur.

sympathetic nervous system; handgrip exercise; phosphocreatine; phosphorous-31-nuclear magnetic spectroscopy; pH; Doppler ultrasound

BLOOD FLOW to resting skeletal muscle is constrained by a high level of sympathetic tone (17). With contractions, vasodilation occurs within the active muscle to augment flow and oxygen transport. This vasodilation is caused, in part, by metabolites released from muscle after contraction (1, 18). Additionally, several mechanisms are activated during exercise that initiate a sympathetic vasoconstrictor response during ischemic or heavy work (8). A number of investigators have suggested that this heightened vasoconstrictor response actively opposes local vasodilatory stimuli, resulting in a reduction in muscle perfusion (10, 23).

In contrast, other studies suggest that the accumulation of metabolites from active skeletal muscle during heavy work inhibits adrenergic effects on vascular smooth muscle (18) and opposes the vasoconstrictor influences of the elevated sympathetic tone (5, 9, 15, 21). For example, Kjellmer (9) and Remensnyder et al. (15) concluded that even maximal sympathetic nerve activation, which resulted in small reductions in blood flow, cannot oppose the vasodilatory stimuli caused by local metabolic changes in active skeletal muscle. These results have prompted investigators to hypothesize that such a functional sympatholysis develops so that muscle perfusion is matched to the metabolic demand (5, 9, 21).

If flow to the working skeletal muscle is preserved by local vasodilatory metabolites, even during heavy exercise, then muscle glycolytic metabolism should be altered minimally in the face of an elevated sympathetic tone. Indeed, Strandell and Shepherd (21) have argued, on the basis of measured forearm blood flow (FBF) and deep venous hemoglobin (Hb) saturation levels during and after exercise, that the reduced oxygen transport with elevated sympathetic tone had minimal metabolic consequences. It was argued that the augmented oxygen extraction compensated for any reductions in flow so that tissue metabolism was unchanged. However, important experiments examining canine limb blood flow have demonstrated that sympathetic activation reduced oxygen uptake in the contracting muscle (23). These findings strongly suggest that heightened sympathetic tone reduces nutritive flow and increases cellular reliance on anaerobic glycolysis.

To date, the effects of elevated sympathetic tone on tissue metabolism during rhythmic exercise have not been assessed. Therefore, the purpose of the present study was to examine the effects of an elevated level of sympathetic tone, evoked by −60 mmHg lower body negative pressure (LBNP), on the metabolic responses of active skeletal muscle during rhythmic handgrip exercise. We hypothesized that the reductions in muscle blood flow accompanying the elevated sympathetic tone would result in a greater reliance on nonoxidative fuel sources and more cellular acidosis. Accordingly, we measured intracellular pH, and phosphocreatine (PCr) with [31P-nuclear magnetic resonance (NMR) spectroscopy] during exercise under conditions of normal and elevated sympathetic tone (LBNP). The results indicated that, although resting muscle metabolism was not affected by the heightened sympathetic tone, intracellular pH during both exercise and recovery was lower with LBNP, an effect that was associated with reductions in FBF and mitochondrial respiration.

METHODS

Subjects

Sixteen healthy subjects (15 men and 1 woman) volunteered for this study. The subjects were 20–43 yr of age (mean age 29.2 yr) and weighed 77.1 ± 3.1 kg (mean ± SE). All
subjects provided informed written consent to the experimental protocol, which was approved by the Human Subjects Protection Office of The Milton S. Hershey Medical Center. All subjects were in good health.

Experimental Design

After assuming the supine position in a nonmagnetic box designed to provide LBNP, the subject was instrumented for heart rate (electrocardiogram), and blood pressure (Dinamap, Tampa, FL). The subject was sealed in the LBNP box at the waist. A maximal voluntary contraction was measured in the nondominant forearm.

Exercise protocol. After at least 5 min of baseline rest, each subject performed 1 min of rhythmic isometric handgrip exercise at each of four increasing workloads. The workloads were 7.5, 15, 22.5 and 30 lbs., corresponding to ~17, 34, 52 and 69% of each subject’s maximal voluntary isometric contraction. The contractions were performed with the nondominant arm in a work-rest schedule of 1 s:1 s. The subjects generated the required force by squeezing the handgrip ergometer, causing a deflection of the potentiometer needle to the desired target. After the cessation of the exercise, 5 min of recovery were observed (Fig. 1). Pilot studies suggested that this paradigm was nearly fatiguing and was associated with significant cellular acidosis.

For investigation of the role of an elevated level of sympathetic tone on the metabolic responses to rhythmic handgrip contractions, the exercise was performed without (Control) and with LBNP to 260 mmHg. LBNP was chosen for the present studies because it elevates the level of sympathetic nervous system (SNS) outflow (5) without altering mean arterial pressure (MAP) (21). This was important because a change in arterial pressure could alter limb blood flow in a manner independent of changes in vascular resistance. The effect of the progressive exercise paradigm was then superimposed on the elevated SNS tone during LBNP. The order of the Control and LBNP trials was varied among subjects. At least 20 min of rest occurred between each trial. LBNP was begun during baseline and continued for 2 min before the handgrip exercise was initiated.

With this design, our goal was to alter muscular metabolism in a graded fashion and thereby grade the amount of metabolite-induced vasodilation. In this manner, we could determine whether heightened sympathetic activation had a greater effect on metabolism at low or high workloads.

Data collection and analysis. The metabolic profile of the contracting forearm skeletal muscle was assessed by using 31P-NMR spectroscopy for analysis of muscle PCr and pH. Measures of the high-energy phosphate content of the exercising flexor digitorum superficialis were obtained with a 1.9-T 26-cm-bore superconducting magnet (Oxford Instruments, Abington, UK) interfaced with a radio-frequency transmitter/receiver (Nicolet Instrument, Madison, WI). A coil 2.5 cm in diameter was placed over the flexor digitorum superficialis muscle. The obtained spectra were collected at 32.5 MHz and represented the Fourier transformation of 32 transients averaged over 60 s at rest, at each exercise workload, and for each minute of recovery. The relative concentrations of PCr were calculated from the area under the resonance curve and are expressed in arbitrary units. Intracellular pH was calculated from the shift of the P resonance relative to PCr. The NMR technique has been described previously (3).

Fig. 1. Schematic presentation of the experimental and exercise protocol performed by each subject. Supine rhythmic handgrip exercise was performed at each of 4 workloads (G1–G4). Exercise was performed for 1 min at each workload in a 1-s work:1-s rest schedule. Five minutes of recovery (R1–R5) followed the exercise. Trials were performed without lower body negative pressure (LBNP; Control) and with LBNP (−60 mmHg).
stored in an ice bath. No more than 45 min passed before these samples were analyzed.

In a subset of subjects, brachial artery diameter (n = 4) and mean blood velocity (MBV; n = 6) data were collected to directly assess the effect of an elevated sympathetic tone on FBF at rest, at each level of exercise, and at each minute of recovery. Brachial artery diameters were measured by using an echo Doppler ultrasound-imaging system (Philips SD-800) and a handheld 7.5-MHz linear probe. Measures were obtained during the last 10 s of each measurement period. MBV was collected by using a 5-MHz continuous-wave Doppler probe (Hokanson CW-1A) that was fixed to the skin over the brachial artery just proximal to the medial epicondyle, where the artery runs parallel to the skin. The continuous MBV data during the last 10 s of each measurement period were averaged to reduce variability associated with muscular contractions and relaxation (16, 20).

Statistics

The effects of LBNP on the metabolic and hemodynamic variables over the course of the exercise trials were assessed by using a repeated-measures two-way analysis of variance. The differences were considered statistically significant if \( P < 0.05 \). When a significant interaction was observed, point-wise comparisons were assessed by using the Student-Newman-Keuls post hoc test. All values are presented as means ± SE.

RESULTS

Intramuscular Metabolism

Significant statistical interactions occurred for both intramuscular PCr and pH across the exercise workload and recovery time points. Intramuscular PCr levels, as a percentage of baseline, were reduced during the exercise (\( P < 0.05 \); Fig. 2). In addition, post hoc analysis showed that at the second and third workloads, as well as at all recovery time points, PCr levels were lower with LBNP compared with Control (\( P < 0.05 \); Fig. 2). Post hoc analysis of cellular pH showed that, compared with the Control trials, exercise with LBNP caused a greater acidosis in the working muscle during the fourth exercise load and throughout the first 4 min of recovery (\( P < 0.05 \); Fig. 2).

Deep Venous Blood Sample Measurements

In the Control trial, Hb saturation was reduced from a rest level of 82.9 ± 3.6 to 52.1 ± 2.6% in the first exercise load (\( P < 0.05 \)) and was maintained at this lower level until the end of exercise (Fig. 3). With LBNP, the exercise Hb-saturation levels were significantly reduced from Control at all workloads (\( P < 0.05 \)). During recovery, Control Hb saturation returned quickly to rest levels. With LBNP, Hb saturation was not different from Control during the first minute after the cessation of exercise. However, LBNP resulted in a reduction in recovery Hb saturation by 5 min after exercise (\( P < 0.05 \)).

In both the Control and LBNP trials, venous pH was reduced from 7.38 ± 0.01 at rest to ~7.33 at the end of the second work period (\( P < 0.05 \) compared with rest). With LBNP, the venous pH was lower than Control at the end of the fourth workload (\( P < 0.05 \)). With LBNP, venous pH remained below Control levels for the duration of recovery (\( P < 0.05 \); Fig. 3).

In conjunction with the venous pH response, blood lactate levels were increased over rest, beginning with the second workload and continuing for the duration of recovery (\( P < 0.05 \); Table 1). LBNP produced an additional increase in blood lactate levels, which were greater than Control for the final exercise workload and for the duration of recovery (\( P < 0.05 \)). Blood-gas analysis showed reductions in venous oxygen pressure (\( \text{PvO}_2 \)) with exercise which were greater during LBNP for the first exercise workload as well as for minutes 3 and 5 of recovery (\( P < 0.05 \); Table 1). Otherwise, \( \text{PvO}_2 \) was similar between Control and LBNP. \( \text{PvCO}_2 \) levels were increased during exercise, relative to rest and recovery (\( P < 0.05 \), but were unchanged by LBNP (Table 1).

Hemodynamic Responses

The HR and MAP responses, obtained during the venous blood sampling and Doppler studies, were qualitatively and statistically similar to the tests conducted during the NMR experiments. By the first measured
Effect of timepoint, after 2 min of LBNP, baseline MAP (92.8 ± 6.6 mmHg) was unchanged from Control (91.7 ± 6.3 mmHg) and during and after rhythmic handgrip exercise (P > 0.05). During LBNP, diameters were 3.6 ± 0.3 and 4.0 ± 0.2 mm at rest and end exercise, respectively, but these were not significantly different from Control (P = 0.07). Compared with Control, MBV was reduced during the LBNP portion of the test (P < 0.001; see Main Effect, Table 2).

DISCUSSION

We have shown that, for the conditions studied, an increase in sympathetic tone was associated with alterations in muscle metabolism during moderate and heavy exercise intensities and during recovery from the exercise. Specifically, intramuscular levels of PCR and pH were reduced, and venous lactate concentrations were increased with exercise during LBNP compared with Control. These data indicate a greater reliance on nonoxidative metabolism during exercise in the presence of heightened sympathetic tone. In addition, the blood pressure response to the exercise and during recovery was not altered by the elevated sympathetic tone so that the reduced Hb saturation, lower recovery PCR levels, and diminished brachial artery MBV with LBNP reflected a reduction in FBF due to sympathetic constriction, rather than a direct effect of LBNP on perfusion pressure or myogenic tone. It appears, therefore, that sympathetic vasoconstriction was not overridden by metabolic vasodilation. Thus, with augmented sympathetic tone, the sympatholytic effects of muscle metabolism did not adjust oxygen transport to match the metabolic demand.

There is a controversy regarding the ability of an augmented sympathetic outflow to vasoconstrict a metabolically active muscle bed, with evidence provided both for (5, 9, 21) and against (6, 14, 19, 24) the hypothesis of sympatholysis. Part of this controversy may be due to differences in the methods used to report muscle perfu-

![Fig. 3. Time course of change in deep venous blood hemoglobin saturation (A) and pH (B) during rhythmic handgrip exercise and recovery was altered during application of LBNP (●); control (○); n = 8 subjects. *Significant difference between groups, P < 0.05.](http://jap.physiology.org/)

Table 1. Effect of −60 mmHg after LBNP on venous effluent blood indexes of muscle metabolism at rest as well as during and after rhythmic handgrip exercise

<table>
<thead>
<tr>
<th>Group (Before LBNP)</th>
<th>Rest</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>R1</th>
<th>R3</th>
<th>R5</th>
<th>LBNP Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.63 ± 0.09</td>
<td>0.65 ± 0.08</td>
<td>0.99 ± 0.09</td>
<td>1.51 ± 0.16</td>
<td>2.27 ± 0.22</td>
<td>2.23 ± 0.26</td>
<td>2.18 ± 0.30</td>
<td>1.68 ± 0.27</td>
<td>P &lt; 0.001</td>
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<tr>
<td>LBNP</td>
<td>0.60 ± 0.09</td>
<td>0.76 ± 0.12</td>
<td>1.31 ± 0.19</td>
<td>1.87 ± 0.22</td>
<td>2.67 ± 0.26*</td>
<td>3.08 ± 0.27*</td>
<td>3.06 ± 0.37*</td>
<td>2.49 ± 0.40*</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Control</td>
<td>37.6 ± 2.3</td>
<td>39.9 ± 2.7</td>
<td>45.1 ± 2.4</td>
<td>54.5 ± 3.5</td>
<td>64.8 ± 5.5</td>
<td>53.1 ± 3.4</td>
<td>43.7 ± 2.6</td>
<td>40.4 ± 2.6</td>
<td>P &lt; 0.05</td>
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<tr>
<td>LBNP</td>
<td>38.3 ± 1.3</td>
<td>41.3 ± 2.1</td>
<td>48.5 ± 2.2</td>
<td>57.7 ± 2.3</td>
<td>70.9 ± 3.2</td>
<td>59.5 ± 3.3</td>
<td>45.6 ± 2.5</td>
<td>41.7 ± 2.1</td>
<td>P &lt; 0.05</td>
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<tr>
<td>Control</td>
<td>53.8 ± 6.0</td>
<td>28.9 ± 1.5</td>
<td>26.9 ± 1.4</td>
<td>28.0 ± 1.2</td>
<td>28.2 ± 1.0</td>
<td>47.5 ± 2.6</td>
<td>52.1 ± 3.8</td>
<td>51.5 ± 4.4</td>
<td>P &lt; 0.05</td>
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<tr>
<td>LBNP</td>
<td>52.1 ± 5.5</td>
<td>22.4 ± 0.7*</td>
<td>23.8 ± 1.1</td>
<td>24.4 ± 1.1</td>
<td>27.0 ± 1.7</td>
<td>49.5 ± 3.3</td>
<td>47.4 ± 3.3*</td>
<td>42.0 ± 3.1*</td>
<td>P &lt; 0.05</td>
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</table>

Values are means ± SE. LBNP, lower body negative pressure (−60 mmHg); P_{\text{VCO}_2}, venous blood pressure of CO2; P_{\text{VO}_2}, venous blood pressure of O2; G1–G4, incrementing intensities of handgrip exercise at 1 min per level; R1, R3, and R5, minutes 1, 3, and 5 of recovery. There is a main effect of exercise for all variables (P < 0.05). Main effect of LBNP is indicated in right column; n = 8 subjects. *Significant difference between Control and LBNP as assessed by post hoc analysis when significant statistical interactions were observed, P < 0.05.
Table 2. Effect of −60 mmHg LBNP on hemodynamic responses at rest as well as during and after rhythmic handgrip exercise

<table>
<thead>
<tr>
<th>Group</th>
<th>Rest</th>
<th>Rest with LBNP</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>R1</th>
<th>R3</th>
<th>R5</th>
<th>LBNP</th>
<th>Effect</th>
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<tr>
<td></td>
<td>Heart rate, beats/ min (n = 8)</td>
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<tr>
<td>Control</td>
<td>64 ± 3</td>
<td>67 ± 2</td>
<td>71 ± 3</td>
<td>75 ± 4</td>
<td>76 ± 4</td>
<td>64 ± 4</td>
<td>63 ± 3</td>
<td>63 ± 3</td>
<td>P &lt; 0.001</td>
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<tr>
<td>LBNP</td>
<td>62 ± 3</td>
<td>80 ± 4*</td>
<td>83 ± 4*</td>
<td>84 ± 4*</td>
<td>89 ± 4*</td>
<td>98 ± 6*</td>
<td>89 ± 6*</td>
<td>87 ± 5*</td>
<td>87 ± 5*</td>
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<td></td>
<td>Mean arterial pressure, mmHg (n = 8)</td>
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<td></td>
<td>NS</td>
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<tr>
<td>Control</td>
<td>93.4 ± 3.2</td>
<td>96.4 ± 2.7</td>
<td>97.8 ± 3.1</td>
<td>103 ± 4</td>
<td>109 ± 5</td>
<td>95.1 ± 5.2</td>
<td>92.1 ± 3.5</td>
<td>91.4 ± 3.3</td>
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<td>LBNP</td>
<td>96.5 ± 3.4</td>
<td>92.8 ± 3.2</td>
<td>95.3 ± 3.8</td>
<td>99.5 ± 3.8</td>
<td>106 ± 4</td>
<td>109 ± 4</td>
<td>94.8 ± 4.5</td>
<td>94.5 ± 2.9</td>
<td>94.5 ± 3.7</td>
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<td>Brachial artery diameter, mm (n = 4)</td>
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<tr>
<td>Control</td>
<td>3.8 ± 0.1</td>
<td>3.8 ± 0.1</td>
<td>3.6 ± 0.3</td>
<td>3.6 ± 0.2</td>
<td>3.7 ± 0.2</td>
<td>3.9 ± 0.2</td>
<td>4.1 ± 0.1</td>
<td>4.0 ± 0.2</td>
<td>3.8 ± 0.1</td>
<td>P &lt; 0.07</td>
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<tr>
<td>LBNP</td>
<td>3.8 ± 0.1</td>
<td>3.6 ± 0.3</td>
<td>3.7 ± 0.2</td>
<td>3.9 ± 0.1</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.2</td>
<td>3.9 ± 0.1</td>
<td>4.0 ± 0.1</td>
<td>3.7 ± 0.1</td>
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<td>Brachial artery mean blood velocity, cm/s (n = 6)</td>
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<tr>
<td>Control</td>
<td>8.97 ± 1.9</td>
<td>16.1 ± 1.3</td>
<td>17.1 ± 2.5</td>
<td>20.9 ± 2.3</td>
<td>23.6 ± 3.0</td>
<td>21.9 ± 2.4</td>
<td>13.8 ± 2.7</td>
<td>12.4 ± 2.5</td>
<td>P &lt; 0.001</td>
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<tr>
<td>LBNP</td>
<td>6.03 ± 1.1</td>
<td>3.11 ± 0.8</td>
<td>11.1 ± 1.5</td>
<td>12.5 ± 1.9</td>
<td>16.4 ± 2.5</td>
<td>20.7 ± 2.2</td>
<td>17.6 ± 2.9</td>
<td>9.41 ± 2.6</td>
<td>7.41 ± 1.8</td>
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</table>

Values are means ± SE. Rest with LBNP levels were obtained after 2 min of lower body suction; n, no. of subjects. There is a main effect of exercise for all variables (P < 0.05). * Significant difference between control and LBNP, as assessed by post hoc analysis of significant statistical interactions between effects of LBNP and handgrip exercise, P < 0.05.

The effect of sympathetic activation under conditions of high blood flow is relatively small if expressed in terms of vascular resistance or blood flow but is much greater if expressed in terms of conductance (13). For example, Kjellmer (9) observed that steady-state changes in vascular resistance with direct sympathetic nerve stimulation became smaller and smaller as blood flow increased in response to electrically induced contractions; Kjellmer concluded that functional sympatholysis had occurred. Rowell (16) expressed the vascular resistance data of Kjellmer (9) to reflect changes in vascular conductance and concluded that sympatholysis had not occurred. Also, other investigators have concluded that sympathetic nervous system retards the ability to reduce vascular conductance in skeletal muscle during sustained exercise (6, 14, 19, 24).

Differences in the magnitude of sympathetic activation may also contribute to the controversy of sympatholysis. As opposed to the −60 mmHg LBNP used in the present study, Hansen et al. (5) used −20 mmHg LBNP and near infrared spectroscopy measures of Hb and myoglobin oxygen saturation in the exercising forearm. They concluded that tissue oxygenation is sustained during even mild intensity handgrip exercise. Finally, an important factor to consider in this controversy may be the baseline level of sympathetic tone. Previous proponents of sympatholysis activated LBNP after steady-state exercise had been achieved (5, 21), whereas, in the present study, exercise was superimposed on a higher level of sympathetic tone induced by LBNP. Whether or not these findings suggest that the total number of microvascular units recruited for a given vasodilatory signal is attenuated with augmented baseline sympathetic tone will require further investigation.

The critical issue regarding the role of sympathetic tone in producing a change in blood flow, vascular conductance, or vascular resistance is the effect on muscle metabolism. Joyner et al. (7) and Thompson and Mohrman (23) have shown that sympathetic activation results in reductions in exercise muscle oxygen uptake at a given workload. These data suggested that enhanced sympathetic tone increased the reliance on nonaerobic sources of energy.

In the present study, venous lactate and pH levels were altered by LBNP, suggesting that skeletal muscle metabolism was altered by the heightened sympathetic tone. However, venous lactate and pH can also be affected by the rate of washout and concentration gradients. Hb saturation data also indicated a reduced flow with LBNP. However, Hb saturation may also be altered by differences in muscle temperature and pH (i.e., the Bohr effect). Accordingly, NMR measures of intramuscular PCr and pH were obtained as direct measures of tissue metabolism. Together, the results of the present study are consistent in showing that, for the conditions studied, sympathetic activation does alter muscle metabolism. Thus the present data support the postulate of previous studies (6, 19, 23) that metabolic vasodilation cannot adequately override sympathetic vasoconstrictor influences during rhythmic exercise. The NMR and venous effluent data suggest that the metabolic impact of enhanced sympathetic tone was greatest at the highest workload when the balance between flow delivery and muscle metabolism would be presumed to be most tenuous.

Although brachial artery diameters were not altered with LBNP, MBV was reduced, indicating a reduction in limb blood flow. Because brachial artery diameters were obtained from a small number of subjects, we did not calculate FBF. However, given the small effect of LBNP on the conduit artery dimensions, it can be expected that the −12% reduction in velocity at end exercise would translate into a similar effect of LBNP on FBF. Because MAP was constant between Control and LBNP trials, the reduction in FBF was due to an increase in downstream resistance, likely secondary to increased sympathetic tone (4). When the velocity...
data are viewed in conjunction with the Hb saturation data, it can be estimated that muscle oxygen uptake was reduced ~20% at end exercise with LBNP. This estimate assumes that LBNP did not change arterial Hb saturation. An important consideration in estimating the reduction in muscle oxygen uptake with LBNP is that our measures of blood gases and Hb saturation were obtained from mixed venous blood representing contributions from active and inactive skeletal muscle as well as from forearm skin with relatively low metabolic activity. Therefore, the oxygen uptake by active muscle may be greater than estimated. How increased sympathetic tone alters flow distribution in the human forearm muscle is unknown. Overall, the altered levels of PCr, the reductions in intramuscular pH, and the venous pH and lactate values are all in line with the measured reductions in tissue perfusion. Therefore, the present data provide both hemodynamic and metabolic evidence that flow to the exercising muscle during and after exercise was reduced by LBNP.

Recovery

During recovery, brachial artery MBV continued to be attenuated by LBNP, although Hb saturation levels were similar during the two trials. These results suggest that during recovery, oxygen consumption was lower during LBNP. This may explain, in part, the lower PCr and hydrogen ion concentrations observed during recovery in the LBNP trial. Parenthetically, it could be argued that an elevated hydrogen ion concentration during recovery with LBNP could have slowed PCr recovery (2, 22). However, the time course of change in PCr, with respect to intramuscular pH, does not support this explanation. The differences in PCr between the Control and LBNP trials became progressively larger as recovery continued, whereas differences in intramuscular pH were greatest early in the recovery phase. PCr recovery depends largely on the oxidative capacity of muscle (11) and has been used to estimate the rate of oxidative metabolism after exercise (22). Therefore, the attenuated levels of PCr during the entire recovery period of the present study suggest that oxygen utilization was diminished after the cessation of contractions, as well as during exercise.

Clinical Implications

Our report demonstrates that the ability to vasodilate a metabolically active muscle bed is attenuated by an augmented sympathetic tone leading to marked alterations in muscle metabolism. It has been hypothesized that blood flow to active skeletal muscle is reduced by vasoconstriction when the individual’s cardiac output has been exceeded by the flow requirements of large muscle mass exercise (16). The present data support this hypothesis and, by inference, suggest that oxygen extraction may not compensate for the reduced flow so that muscle metabolism is altered. From a clinical standpoint, patients with congestive heart failure are known to have elevated sympathetic tone at rest. Concurrently, exercise tolerance is attenuated in these individuals due to premature fatigue relative to normal controls. It is not known whether the decreased exercise tolerance is due to alterations in skeletal muscle function (12), to limitations in cardiac output, to reductions in limb perfusion, or to a combination of these effects. Based on the results of the present study, it is hypothesized that the elevated sympathetic tone associated with heart failure may evoke prominent vasoconstriction in active muscle beds, thereby further impeding vasodilation and leading to premature cellular acidosis and fatigue.

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Address for reprint requests: L. I. Sinoway, Div. of Cardiology, The Milton S. Hershey Medical Center, PO Box 850, Hershey, PA 17033.

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REFERENCES

11. McCully, K. K., K. Vandenbome, K. DeMeirleir, J. D. Posner, and J. S. Leigh, J. R. Muscle metabolism in track athletes,


