Evidence for sympatholysis at the onset of forearm exercise

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Received 22 March 2002; accepted in final form 2 May 2002

DeLorey, Darren S., Simon S. Wang, and J. Kevin Shoemaker. Evidence for sympatholysis at the onset of forearm exercise. J Appl Physiol 93: 555–560, 2002. First published May 3, 2002; 10.1152/japplphysiol.00245.2002.—The effect of augmented sympathetic outflow on forearm vascular conductance after single handgrip contractions of graded intensity was examined to determine whether sympatholysis occurs early in exercise (n = 7). While supine, subjects performed contractions that were 1 s in duration and 15, 30, and 60% of maximal voluntary contraction (MVC) in intensity. The contractions were repeated during control and lower body negative pressure (LBNP) (~40 mmHg) sessions. Forearm blood flow (FBF; Doppler ultrasound) and mean arterial pressure were measured continuously for 30 s before and 60 s after the single contractions. Vascular conductance (VC) was calculated. Total postcontraction blood flow increased in an exercise intensity-dependent manner. Compared with control, LBNP caused a reduction in baseline and postexercise FBF (P < 0.05), VC (P < 0.01), as well as total excess flow (P < 0.01). Specifically, during LBNP, baseline FBF and VC were reduced by 29 and 34% of control, respectively (P < 0.05). After the 15% MVC contraction, peak VC during LBNP was reduced by a magnitude similar to that during baseline (i.e., ~30%), but it was only reduced by 15% during both the 30 and 60% MVC trials (P < 0.01). It was concluded that the stimuli for exercise hyperemia during moderate and heavy, but not mild, handgrip exercise intensities, diminish the vasoconstrictor effects of LBNP. Furthermore, these data demonstrate that this sympatholysis occurs early in exercise.

Doppler ultrasound; forearm blood flow; vascular conductance; lower body negative pressure; sympathetic nervous system

DESPITE CONSIDERABLE RESEARCH, the mechanisms responsible for the control of muscle blood flow at the onset of exercise remain elusive. Vascular tone at rest and during exercise is determined by the ability of vascular smooth muscle to integrate competing vasodilatory and vasoconstrictor signals from endothelial, metabolic, and neurogenic sources. At the onset of exercise, the early increase in muscle blood flow has been attributed to the muscle pump and an early rapid vasodilation (8, 28, 33). However, attempts to identify the substance(s) responsible for this early vasodilation have not been successful (34), and thus the search for an alternative explanation is warranted. The ability of the sympathetic nervous system to restrain blood flow to active skeletal muscle has been an active area of investigation. Several studies have demonstrated that there is sympathetic vasoconstriction in active skeletal muscle (4, 14, 21, 22, 27), and O’Leary et al. (21) have argued that sympathetic activity directed to active skeletal muscle increases as exercise intensity increases.

Conversely, other investigations have demonstrated an attenuation of vasoconstriction in active skeletal muscle during exercise (5, 24). This diminished vascular responsiveness to sympathetic stimulation was termed “sympatholysis” by Remensnyder et al. (24). Presynaptic inhibition of neurotransmitter release from the nerve terminal or an attenuation of postjunctional adrenergic-receptor responsiveness are both potential mediators of sympatholysis (5, 31). The metabolic attenuation of α-adrenergic constriction is intensity dependent, being more clearly observed during heavy contractions (5, 31). On the basis of these observations, Thomas et al. (31) proposed that a certain level of glycolytic activity is necessary to attenuate sympathetic vasoconstrictor activity.

Although these earlier studies (5, 24, 31) have demonstrated the presence of functional sympatholysis during graded exercise and have attempted to identify a mechanism, they have not focused on the temporal aspects of this response. Specifically, it is not known whether sympatholysis is present early in exercise and involved in the regulation of blood flow at the onset of contractions. Previously, it was reported that the constrictor influence of the sympathetic nervous system could constrain muscle blood flow at the onset of exercise in humans (27). How this impacts on the early and rapid vasodilation that our laboratory (28, 33) and others (1, 8) have observed at the exercise onset is not known. Therefore, the purpose of this study was to test the hypothesis that sympatholysis occurs at the exercise onset. On the basis of the above evidence, it was reasoned that if sympatholysis does occur early in

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exercise, then the ability of the sympathetic vasoconstrictor effect of lower body negative pressure (LBNP) to reduce forearm vascular conductance after a single contraction would be greater during mild than heavy contractions.

METHODS

Subjects. Seven healthy subjects (6 men, 1 women) were recruited for participation in this study. The mean age of the subjects was 23 ± 4 (SD) yr, height was 170 ± 11 cm, and weight was 72 ± 6 kg. Subjects were informed of all testing procedures and any risks and discomforts associated with testing before giving their informed consent to participate. The University of Western Ontario ethics committee for research on human subjects approved all procedures.

Protocol. All testing was performed with the subjects in the supine position, and the arm was maintained above heart level to diminish muscle pump contributions (28, 33). Subjects were sealed in a LBNP chamber at waist level. Two maximal voluntary contractions (MVCs) were performed, the largest of which was used to determine the relative intensity of all other contractions used during the protocol. During the tests, subjects performed single, handgrip contractions at 15, 30, and 60% of MVC with the target force displayed on an oscilloscope. Each contraction was 1 s in duration and was followed by a 2-min recovery period. Subjects performed a minimum of three contractions at each exercise intensity. To examine the balance between sympathetic outflow and metabolic regulators of vascular tone during exercise, we utilized LBNP to exert sympathetically mediated control over forearm vasomotor tone (17, 29). The control and LBNP (~40 mmHg) trials were varied across subjects, and, within each condition, the order of contraction intensity was randomly assigned. Approximately 20 min of rest separated the control and LBNP testing sessions. During LBNP, suction was applied for 3 min before baseline measurements.

Measurements. Mean arterial pressure (MAP) was measured continuously by finger-cuff plethysmography (Finapres, Ohmeda) on the middle finger of the nonexercising hand that was maintained at heart level. Heart rate (HR) was monitored continuously by electrocardiogram. Brachial artery mean blood velocity (MBV) was measured beat by beat with Doppler ultrasound (GE/Vingmed System Five, 5 MHz). All analog signals were sampled and recorded in real time at 100 Hz (PowerLab, ADInstruments) and stored on a computer for subsequent analysis. Brachial artery diameter was measured by using B-mode echo Doppler imaging (GE/Vingmed System Five, 10 MHz) with measures made in triplicate at rest during both control and LBNP conditions.

Calculations. The beat-by-beat MBV, HR, and MAP data for each repeated trial were averaged for each subject to obtain a representative response for each exercise intensity and condition. Beat-by-beat forearm blood flow (FBF) was calculated as the product of MBV and the vessel cross-sectional area (πr²), where r is the vessel radius. Vascular conductance (VC) was calculated as VC = FBF/MAP. This value best accounts for changes in vasomotor tone under conditions where blood flow changes dominate changes in arterial blood pressure (16).

Total postcontraction blood flow was calculated by summing the blood flow per beat from the release of the contraction until blood flow had returned to baseline levels. Total excess flow (TEF) was calculated as the sum of flow above baseline over the postcontraction period.

Data analysis. Data collected during LBNP trials were expressed as a percentage of the absolute response determined under control conditions. It was reasoned that, if sympatholysis was involved in the early vasomotor response after a contraction, then the ability of LBNP to reduce VC (i.e., relative to control) should be less after the contraction than at rest. Moreover, if sympatholysis was graded with exercise intensity, then the diminished effect of LBNP on VC after each contraction should be greater with the heavier exercise intensities. The effect of LBNP on baseline variables was determined by paired t-test. Differences in peak and TEF responses across contraction intensities were determined by repeated-measures ANOVA. An α level of 0.05 was used to determine statistical significance in all cases. Data are presented as means ± SE.

RESULTS

Baseline values. MAP was 70 ± 2 mmHg in control and 79 ± 4 mmHg during LBNP (P = 0.07). The vasoconstrictive effect of LBNP on baseline values is shown in Fig. 1. Group data for baseline FBF and VC during control and LBNP before the onset of contraction at each exercise intensity are illustrated in Fig. 1, A and B, respectively. FBF during LBNP was reduced to 71 ± 2% of control (82 ± 13 vs. 66 ± 10 ml/min for

![Fig. 1. Baseline forearm blood flow (FFB; A) and vascular conductance (B) during control and lower body negative pressure (LBNP) conditions before 15, 30, and 60% maximal voluntary contraction (MVC). *P < 0.05 vs. control.](http://www.jap.org)
control vs. LBNP; \( P < 0.01 \). Subsequently, baseline VC was reduced to 66 ± 2% of control (1.18 ± 0.17 vs. 0.85 ± 0.13 ml·min\(^{-1} \)·mmHg\(^{-1} \) for control vs. LBNP, respectively; \( P < 0.01 \)).

**Peak FBF and VC.** Peak postcontraction hyperemia was graded in an intensity-dependent manner in both control and LBNP conditions (Fig. 2A). In LBNP, the peak FBF response (% of control) at 15% MVC was reduced by a magnitude similar to that observed during baseline conditions (i.e., ~25% reduction) (Fig. 2B). However, at both the 30 and 60% MVC workloads, the peak FBF response was only reduced to 12% of control (Fig. 2B; \( P < 0.05 \) vs. 15% MVC). The peak FBF during LBNP expressed as a percentage of control values was not different at 30 and 60% MVC.

Peak VC followed a pattern similar to FBF, demonstrating dependency on exercise intensity and being reduced in LBNP vs. control (\( P < 0.05 \); Fig. 3A). Also, at 15% MVC, peak postcontraction VC during LBNP vs. control was reduced by a magnitude similar to that observed at baseline (30%), whereas a smaller reduction of 15% was observed during both the 30 and 60% MVC trials (\( P < 0.01 \) vs. 15% MVC; Fig. 3B).

**Total FBF and TEF.** Compared with control, total postcontraction FBF was reduced during LBNP (Fig. 4A). However, the magnitude of this effect was dependent on exercise intensity. Specifically, the LBNP effect on total postcontraction FBF (% of control) at 30 and 60% MVC was less than at 15% MVC (\( P < 0.05 \)). However, the LBNP-induced reduction in total postcontraction FBF was not different after the 30 and 60% MVC exercise (Fig. 4B).

Similarly, TEF was reduced in LBNP compared with control at each exercise intensity (Fig. 5A). However,
The LBNP effect on TEF, expressed as a percentage of control, was exercise intensity dependent with TEF at 30 and 60% MVC being greater than TEF at 15% MVC (P < 0.01; Fig. 5A). There was no difference in TEF (% of control) at 30 and 60% MVC.

**DISCUSSION**

The results of this study demonstrate that the stimuli for exercise hyperemia during moderate- and heavy-intensity, but not mild-intensity, exercise diminish the vasoconstrictor effects of LBNP. Furthermore, these data demonstrate for the first time that sympatholysis occurs in response to a single contraction and suggest that this effect may be involved in the regulation of vascular tone (3). Therefore, it is argued that the approach used in the present study reflects the ability of exercise-induced changes in tone to overcome the vasoconstrictor effects of LBNP (i.e., sympatholysis).

The presence of vasoconstriction in active skeletal muscle is arguably important for the prevention of hypotension during heavy exercise (12, 21, 25). However, it is becoming clear that the magnitude of this vasoconstriction is modified by the local metabolic status of the perfused skeletal muscle (3). Specifically, several studies (5, 24, 31) have established that sympatholysis does occur during dynamic exercise and that from differing baseline values in each condition would yield misleading results. In addition, the examination of the absolute change in VC from differing baseline blood flows may poorly represent changes in vessel diameter and lead to inappropriate conclusions related to the regulation of vascular tone (3). Therefore, it is argued that the approach used in the present study reflects the ability of exercise-induced changes in tone to overcome the vasoconstrictor effects of LBNP (i.e., sympatholysis).

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it does so in an exercise intensity-dependent manner. The additional issue addressed in the present study was the examination of blood flow control at the exercise onset. In concert with the earlier data, the present results support the concept that sympatholysis is dependent on the exercise intensity. Specifically, handgrip exercise of 30% MVC or greater resulted in an attenuation of the vasoconstrictive effect of LBNP. However, exercise at 15% MVC showed no evidence that the vasoconstrictor effect of LBNP was different from the precontraction baseline. These present findings support those of Hansen et al. (11), who reported the abolition of LBNP effects on forearm oxygenation at 20% MVC but not 10% MVC rhythmic handgrip contractions. Taken together, the accumulating data suggest that a threshold exercise intensity may be required for sympatholysis to be observed.

Functional sympatholysis appears to be mechanistically related to postjunctional α-adrenergic-receptor responsiveness because the vasoconstrictor effects of norepinephrine infusions and sympathetic nerve stimulation were abolished by muscle contractions (31). Similarly, infusion of α-adrenergic antagonists have demonstrated that receptor responsiveness is diminished in exercising muscle (3). α-Adrenergic receptors are sensitive to the chemical environment of the muscle and may play a role in blood flow distribution (18, 19, 30). More specifically, in both dogs (5) and rats (31), α2-adrenergic receptors appear to be the major site for inhibition of sympathetic constriction during exercise (5). However, the mechanism by which vascular adrenergic receptors are desensitized in exercising skeletal muscle remains uncertain. Earlier observations of greater sympatholysis in the rat gastrocnemius vs. soleus muscle (31) raises the possibility of a fiber type-specific metabolic link between contractions and inhibition of sympathetic constriction. However, adrenergic constriction was not altered during reactive hyperemic conditions despite high metabolic vasodilatory stimuli (11). The observation in the present study that the reduction in forearm vasoconstriction occurred after a single contraction suggests that neither glycolytic metabolism nor acidosis is a required factor. In support of this conclusion, it is noted that the onset of glycolysis is delayed in rhythmic contractions by >20 s (7, 9). Rather, it is expected that the energy to support the 1-s handgrip exercise was primarily derived from immediately available ATP and creatine phosphate stores, with consequent cellular alkalinization (15). Although tissue hypoxia has been implicated in this response (10), it is unlikely that a single contraction of 1-s duration resulted in muscle ischemia or hypoxia or alterations in muscle temperature that could affect metabolism or vascular function.

Nonetheless, the intensity-dependent nature of sympatholysis points to a mechanism that is in some way related to muscle fiber recruitment and/or force development. Additional factors associated with early exercise hyperemia that affect adrenergic neurovascular function may include adenosine, potassium, endothelial-derived nitric oxide, and acetylcholine (20, 26). Of these, nitric oxide, but not acetylcholine, was observed to contribute in a small but significant manner to the total hyperemic response after a single contraction (2), possibly through inhibition of sympathetic vasoconstriction (6). It may be that nitric oxide exerts a postjunctional sympatholytic effect by acting through changes in the activity of ATP-sensitive potassium channels in vascular tissue (32). Interstitial potassium levels can change quickly in response to muscle depolarization (13). However, it remains to be determined whether interstitial potassium is exerting its effect directly on vascular smooth muscle (23) or through desensitization of adrenergic receptors.

In conclusion, the results of this study demonstrate that sympatholysis occurs early in exercise and in an exercise intensity-dependent manner. These data suggest that the attenuation of tonic sympathetic vasoconstrictor tone directed toward the vasculature of active skeletal muscle may be involved in the regulation of blood flow at the onset of moderate- to heavy-intensity exercise.

The authors thank A. Caldwell for assistance during data collection.

This study was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Grant (to K. Shoemaker). D. S. DeLorey was the recipient of a PGIs B doctoral research scholarship from NSERC. S. Wang received a summer research scholarship from NSERC.

REFERENCES


