Skeletal Muscle Metaboreceptor Stimulation Opposes Peak Metabolic Vasodilation in Humans

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The total blood flow requirements of a large muscle mass can exceed the maximal cardiac output generated by the heart during exercise. Therefore, to maintain blood pressure, muscle vasodilation must be opposed by sympathetic vasoconstriction. The primary neural signal that increases sympathetic outflow is unclear. In an effort to isolate the vasoconstricting mechanism that opposes vasodilation, we measured the peak forearm vascular conductance response after the release of 10 minutes of forearm circulatory arrest under five separate study conditions: 1) no leg exercise, 2) low-level supine leg exercise, 3) low-level supine leg exercise with leg circulatory arrest after exercise, 4) high-level supine leg exercise, and 5) high-level supine leg exercise with leg circulatory arrest after exercise. We found that both high-workload conditions reduced peak forearm conductance below the no-leg exercise condition (a 34% reduction during leg exercise and a 52% reduction during leg exercise followed by leg circulatory arrest). In addition, at each workload, leg circulatory arrest after exercise, which isolated the skeletal muscle metaboreceptor contribution to vasoconstriction, reduced forearm conductance by approximately 20% below the values noted for leg exercise alone (combined central command and metaboreceptor stimulation). In a separate group of subjects, peak forearm blood flow was measured during lower-body negative pressure to levels up to −40 mm Hg, a maneuver that unloads high- and low-pressure baroreceptors. This intervention did not affect peak forearm blood flow. We conclude that 1) metaboreceptor stimulation is the crucial mechanism causing the vasoconstriction that opposes metabolic vasodilation, 2) some volitional influence during exercise acts to oppose metaboreceptor-mediated constriction, and 3) baroreceptor unloading does not influence maximal forearm conductance. (Circulation Research 1990;66:1576–1584)

A lam and Smirk first demonstrated that if circulatory arrest of exercising muscle is initiated during or immediately before the end of exercise, the resultant blood pressures are higher than resting values. It was postulated by these authors that the accumulation of ischemic metabolites stimulated sensory nerves within skeletal muscle and triggered a pressor reflex. Traditionally, this reflex has been viewed as a system that acts to increase blood flow to exercising skeletal muscle; that is, it has been assumed that vasoconstriction does not occur in metabolically active muscle beds. This would be consistent with studies that have suggested that the metabolites that cause vasodilation can override sympathetic vasoconstriction and cause a functional sympatholysis.

However, it has recently been suggested that in humans heavy exercise by a large percentage of total body muscle mass can lead to muscle flow requirements that exceed the maximal cardiac output. Thus, if vasodilation to active muscle were unopposed, blood pressure would drop. This strongly suggests that vasoconstriction in metabolically active skeletal muscle must occur. The afferent signal for this vasoconstriction is unknown, although it has recently been postulated that skeletal muscle metaboreceptor stimulation may be responsible.

In this report, we examined whether stimulation of metaboreceptors within skeletal muscle would actually cause a vasconstrictor response that was capable of opposing a potent metabolic vasodilator stimulus, a metabolic stimulus of a magnitude similar to

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that seen with vigorous physical exercise. To separate the presumed metabolic vasodilator and vasoconstrictor stimuli that would occur during exercise, we performed leg exercise at two workloads with and without leg circulatory arrest after exercise (vasoconstrictor stimulus) and simultaneously examined changes in forearm blood flow and vascular conductance in response to 10 minutes of forearm circulatory arrest (vasodilator stimulus). Our results suggest that metaboreceptor stimulation causes a workload-dependent vasoconstriction that opposes peak metabolic vasodilation. Moreover, our results provide evidence that metaboreceptor stimulation may be crucial in preventing muscle vasodilation from outstripping maximal cardiac output.

Subjects and Methods

Study Design

Seven healthy male subjects ranging in age from 24 to 35 years (29±2 years) were studied. All subjects were in good health, and none took medication. All subjects signed an informed consent form that was approved by the Hershey Medical Center Clinical Investigation Committee. Before the 4 days of forearm blood flow and exercise measurements, systemic oxygen consumption at the maximum workload (max \( V_O_2 \)) was measured during a progressive upright bicycle ergometer test.

The overall plan of the study was to examine two different levels of exercise to grade metaboreceptor and central volitional influences. At both levels of exercise two study conditions, leg exercise and leg circulatory arrest after exercise, were used in an effort to isolate metaboreceptor influences.

The ability of these various conditions to cause a vasoconstrictor stimulus capable of opposing peak metabolic vasodilatation was then tested. This was accomplished by measuring the peak forearm vascular conductance response that followed the release of 10 minutes of forearm circulatory arrest (peak reactive hyperemic blood flow [RHBf]) during each of these separate exercise conditions (Figure 1). Thus, peak forearm blood flow response was measured during four protocols: 1) 12 minutes of supine leg exercise at 25% max \( V_O_2 \) (25% protocol), 2) approximately 9 minutes of supine leg exercise at 25% max \( V_O_2 \) followed by 2 minutes of two-legged circulatory arrest (25%+CA protocol), 3) 11–12 minutes of supine leg exercise at 75% max \( V_O_2 \) (75% protocol), and 4) approximately 9 minutes of supine leg exercise at 75% max \( V_O_2 \) followed by approximately 45 seconds to 2 minutes of leg circulatory arrest (75%+CA protocol). For all four protocols, leg exercise was begun at the time of forearm circulatory arrest. For the leg circulatory arrest studies, leg occlusion took approximately 5–10 seconds. The subjects then stopped pedaling, and their legs were placed flat on the exercise table. Approximately 20 seconds later, forearm arterial occlusion was released, and forearm blood flows were measured (see below). The 25% protocol was always performed first to determine if the subjects could tolerate the least stressful protocol. We reasoned that if a subject could not tolerate this intervention, he would be unable to tolerate either circulatory arrest after exercise or exercise at 75% max \( V_O_2 \). The 75%+CA protocol was performed last in six of seven subjects. In addition, on each of these 4 days of study, the RHBf was measured without leg exercise.

In six separate subjects (mean age, 29±2 years; range, 29–35 years), we examined the influences of lower-body negative pressure (LBNP) at −15 and −40 mm Hg on peak forearm vascular conductance. This was done to examine directly the effects of the removal of tonic baroreceptor activity peak forearm blood flow. LBNP was begun 7 minutes after forearm arterial occlusion was begun. The sequence during LBNP study was 1) peak forearm blood flow without LBNP, 2) peak forearm blood flow during −15 mm Hg LBNP, 3) peak forearm blood flow during −40 mm Hg LBNP.
In an additional six subjects (mean age, 27 ± 2 years; range, 23–36 years), the effects of leg circulatory arrest alone on peak forearm blood flow were determined. In these studies, leg arrest was begun approximately 20 seconds before the release of forearm arterial occlusion.

Max \( \dot{V}O_2 \) Determination

In all seven subjects, an incremental workload protocol using an upright bicycle ergometer (Collins, Braintree, Massachusetts) was used to determine the max \( \dot{V}O_2 \). The workload was increased by 50 W every 3 minutes until fatigue. The heart rate was monitored by electrocardiogram. Oxygen consumption was measured with a Beckman metabolic cart (model MMC1, Sensormedics, Anaheim, California). Expired \( O_2 \) was measured with a polarographic analyzer, and \( CO_2 \) measurements were performed by an infrared analyzing system. Both \( O_2 \) and \( CO_2 \) analyzers were calibrated using two standard gas calibration tanks (Sensormedics). The metabolic cart was recalibrated after every other 3-minute workload during the entire exercise test. Minute \( O_2 \) consumption, minute \( CO_2 \) production, and total ventilation were recorded every 30 seconds. The ventilatory gas exchange ratio was defined as minute \( CO_2 \) production divided by minute \( O_2 \) consumption.

Forearm Blood Flow Measurements and Supine Leg Exercise

Subjects reported to the human research laboratory in the postabsorptive state. The subjects were placed supine on the exercise table (see below). Forearm blood flows were measured with the venous occlusion technique. The left forearm of each subject was studied. The midforearm was raised approximately 10 cm above the heart; the wrist and elbow were supported, and the midforearm was free. A single-strand, mercury-in-Silastic strain gauge was placed 7 cm below the olecranon process. The gauges were externally calibrated before being placed on the forearm. A rapidly inflatable occlusion cuff was placed on the upper arm; the venous occlusion pressure was 50 mm Hg. A separate occlusion cuff was placed at the wrist. Before any flow measurement, the hand circulation was arrested for at least 1 minute. A 1-minute period of forearm arterial occlusion was then performed since prior studies have shown that the first in a series of peak flow measurements is the lowest. The blood flow response to 10 minutes of circulatory arrest (RHBF) was then measured. Previous studies have shown this to be a stimulus sufficient to produce maximal metabolic forearm vasodilation. Upon release of arterial occlusion, temporary venous occlusions were performed at 5–8 seconds, 15 seconds, and every 15 seconds after release for 2 minutes. The peak flow was always determined within 30 seconds of the release of arterial occlusion. After the dissipation of forearm paresthesias, forearm occlusion was initiated again, and one of the four supine exercise protocols was begun. The supine leg exercise protocols (25%, 25% + CA, 75%, 75% + CA) were performed on a cardiac stress testing system (Engineering Dynamics, Lowell, Massachusetts). The subjects performed exercise at approximately 60 rpm. Upon release of forearm occlusion, blood flows were measured in the same manner as described above. Mean blood pressures (MAPs) were measured in the opposite forearm with an automated device that employed the oscillometric method (Dinamap, Tampa, Florida). The MAPs were determined at the approximate time of the release of forearm circulatory arrest and then every 15–20 seconds. Blood flows are presented as milliliters per minute per 100 ml, and forearm vascular conductance (forearm blood flow divided by MAP) is expressed as milliliters per minute per 100 ml divided by millimeters mercury. For the vascular conductance measurements, MAP closest in time to the flow measurements was used in the calculations.

Since our measurements of forearm conductance in the above protocol were dependent on indirect measurements of MAP, we performed additional experiments validating this noninvasive method during supine exercise. In two subjects, MAP measured by this indirect method was compared with direct intraarterial catheter measurements. A 20-gauge sterile catheter was placed in the radial artery, and noninvasive blood pressure was measured in the opposite forearm. The arterial catheters were filled with heparinized saline and attached to calibrated pressure transducers placed at the midchest level (American Edwards, Irvine, California). In these experiments, MAP was compared during baseline and supine exercise at 50, 100, 150, and 200 W of work.

Statistical Analysis

The effects of the various exercise regimens on the various parameters (blood flow, conductance, MAP) were evaluated using an analysis of variance for repeated measures within an individual. When a significant \( F \) value was found, post hoc analysis was performed with the Newman-Keuls method. Day-to-day variability of the various parameters during RHBF without exercise was analyzed in a similar manner. A value of \( p < 0.05 \) was considered statistically significant. All values are presented as mean ± SEM.

Results

Noninvasive Blood Pressure Validation

The MAP measured by the oscillometric method (indirect method) showed a strong correlation with blood pressure obtained by radial artery catheter with an \( r \) value of 0.98 (\( p < 0.001 \)) (Figure 2).

Oxygen Consumption Data

Max \( \dot{V}O_2 \) was 45.3 ± 3.4 ml/kg/min. The heart rate at end exercise was 175 beats/min (92% of predicted), and the respiratory quotient was 1.01 ± 0.02. The maximal workload was 225.0 ± 15 W. The mean work-
loads used for the 25% and 75% protocols were 56±4 W and 168±11 W, respectively.

Hemodynamic Data

The MAP, peak forearm blood flow, and vascular conductance responses obtained without leg exercise on the four separate study days of the primary experiment were not different. There were no significant sequence effects for any of the three parameters. Because of this, the data obtained during forearm occlusion without leg exercise obtained on the four separate days of study were averaged. These averaged values were then used in our statistical analysis and are presented as the respective “baseline” responses to 10 minutes of forearm circulatory arrest.

MAP During Peak Forearm Blood Flow

Figure 3 shows the mean data for MAP (as well as RHBF and forearm conductance) during the various exercise conditions for the seven subjects. MAP was higher during the 75% and 75%+CA protocols than during RHBF without leg exercise. At each workload, leg circulatory arrest did not change the MAP response. Based on the regression equation in Figure 2, our reported pressures may be underestimated by approximately 4 mm Hg at the higher workload.

Peak Forearm Blood Flow

Peak blood flow values obtained during the 25%+CA and 75%+CA protocols were lower than values obtained during the 25% and 75% protocols. When compared with “baseline” levels of peak flow, only the values at the 75%+CA protocol were lower (Figure 3). This represented a 34% reduction in peak flow. In addition, it should be noted that the RHBF value during the 75%+CA protocol was lower than the value during the 25%+CA protocol, a finding consistent with greater metabolic stimulation at the higher workload. Representative blood flow tracings are shown during baseline and the 75%+CA protocol in Figure 4.

Forearm Conductance

Both the 75% and 75%+CA protocols led to lower vascular conductances than noted during forearm arterial occlusion without leg exercise. The reduction noted during the 75%+CA protocol represented 52%. In addition, conductance during the 75%+CA protocol was statistically lower than at the 25%+CA protocols. Finally, the peak forearm conductance values during the 25%+CA and 75%+CA protocols were lower than values obtained during the respective levels of leg exercise alone. The reduction in conductance attributable to the leg circulatory arrest was 19% at the low workload (25% vs. 25%+CA) and 21% at the high workload (75% vs. 75%+CA). The potential error in conductance measurements due to the use of noninvasive pressures should be 5% or less under all study conditions.

Changes in forearm vascular conductance over the 90 seconds after the release of arterial occlusion are shown for each of the five study conditions in Figure 5 (no leg exercise and the four protocols). The rate of reduction in vascular conductance shown by the curve for no leg exercise and the curve for the 25% protocol seem relatively similar. However, each successive curve thereafter shows a trend toward a more rapid reduction in forearm conductance.

LBNP and Leg Occlusion Studies

LBNP had no effect on peak forearm blood flow. This was true at both −15 and −40 mm Hg. Baseline RHBF was 54.3±5.3 ml/min/100 ml; during LBNP at −15 mm Hg, 52.0±7.3 ml/min/100 ml; during LBNP at −40 mm Hg, 46.8±6.6 ml/min/100 ml (F=1.17, 2, and 10; p=NS). Not surprisingly, LBNP to −40 mm Hg was associated with a 7–mm Hg reduction in mean MAP. Thus, conductance during LBNP of −40

![Figure 2. Graph comparing the mean arterial blood pressure obtained by the oscillometric method (indirect method) with mean arterial blood pressure obtained by indwelling arterial catheters placed in the opposite radial artery (direct method). In these experiments, pressures were compared at rest, during 50, 100, 150, and 200 W of supine exercise in the two subjects. The r value for this comparison is 0.98 (p<0.001). The dotted line represents the line of identity (y=x), and the solid line represents the regression equation. Squares, values at each of four exercise levels and rest for two subjects.](image-url)
A representative graph showing the mean arterial blood pressure (MAP), peak reactive hyperemic blood flow (RHBF), and conductance responses during the five conditions: BASE, responses after 10 minutes of forearm circulatory arrest without leg exercise; 25%, responses after 12 minutes of supine leg exercise at 25% maximum VO₂; 25%+CA, responses after 9 minutes of supine leg exercise at 25% maximum VO₂; 75%, responses after 11-12 minutes of supine leg exercise at 75% maximum VO₂; 75%+CA, responses after 9 minutes of supine leg exercise at 75% maximum VO₂ followed by 45 seconds to 2 minutes of CA. Of note, MAP was higher than base during 75% and 75%+CA. Forearm RHBF and conductance showed both a workload effect (25%+CA vs. 75%+CA) and an effect of circulatory arrest at each workload (25% vs. 25%+CA and 75% vs. 75%+CA). Bars above columns represent SEM. *p<0.05 for comparisons with BASE (analysis of variance within subject comparisons).

Discussion

In the present paper, we have postulated that two opposing forces would control skeletal muscle blood flow during exercise. The first is the dilatory response to exercise that is presumably mediated by an increase in ischemic metabolites. The second is a reflex vasoconstriction whose afferent limb originates in the exercising skeletal muscle. Thus, it was hypothesized that skeletal muscle metaboreflex activation would vasoconstrict metabolically active muscle beds in an effort to prevent blood flow demand from exceeding blood flow supply.

To examine this postulate, we separated the local vasodilating and vasoconstricting influences by providing a “pure” vasodilator stimulus to the forearm, 10 minutes of forearm circulatory arrest, while having the subjects perform the various leg exercise regimens that were designed to increase sympathetic tone. Previous studies in our laboratory have shown that after the release of a 10-minute forearm circulatory arrest, plethysmographically determined forearm blood flow was maximal. However, circulatory arrest for periods up to 20 minutes did not cause a reflex rise in heart rate, MAP, or calf vascular resistance. Thus, 10 minutes of forearm circulatory
arrest causes a large amount of vasodilation without activating the sympathetic nervous system. To increase sympathetic tone, we chose two workloads: 25% max VO$_2$ and 75% max VO$_2$. The workloads were normalized for the max VO$_2$ because plasma norepinephrine, an index of sympathetic activation, correlates better with the percent of maximal workload than with the absolute workload. Because of this finding, we believed that the degree of sympathetic stimulation (at each workload) would tend to be more comparable in the different subjects.

During exercise, multiple neural systems are triggered and initiate a pattern of sympathetic discharge that is related to the level of exercise. These multiple neural inputs include 1) the stimulation of mechanoreceptors and metaboreceptors in skeletal muscle, 2) potential changes in baroreceptor activity during exercise, and 3) increased central volitional influences (central command) during exercise. In this paper, we postulated that changes in forearm conductance after the release of forearm circulatory arrest during 25% max VO$_2$ and 75% max VO$_2$ workloads would provide information regarding the sum of the vasoconstrictor effects due to the above mechanisms at the two different workloads.

It is believed that the sympathetic response due to metaboreceptor stimulation can be separated and isolated if circulation to muscle is arrested seconds before the end of exercise. Recent studies in human subjects using $^3$P nuclear magnetic resonance spectroscopy have suggested that the initiation of this reflex may be linked to skeletal muscle cellular acidosis. Thus, in our present series of experiments, we suspected that any hemodynamic effects observed during the 25%+CA and 75%+CA protocols would be due to stimulation of metaboreceptors within the exercising muscle. We also postulated that the metaboreceptor-induced vasoconstricting influences would be greater at the 75%+CA protocol than at the 25%+CA protocol since the response to circulatory arrest after exercise should be greater at the higher workload; that is, the production of lactic acid and other potential vasoconstricting metabolites should be greater at the higher workload.

**Study Findings**

There are several findings in the present paper worthy of mention: 1) Vigorous leg exercise (at 75% max VO$_2$) reduced the forearm vascular conductance response below values noted during the baseline study condition. 2) Leg circulatory arrest, which isolated efferent activity due to metaboreceptor stimulation, reduced forearm conductance below values during exercise alone. This was true for both the low and high workloads. 3) Leg circulatory arrest after

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**FIGURE 5.** Graph showing the time course of changes in forearm conductance after the release of forearm circulatory arrest. 25%, responses after 12 minutes of supine leg exercise at 25% maximum VO$_2$; 25%+CA, responses after 9 minutes of supine leg exercise at 25% maximum VO$_2$ followed by 2 minutes of leg circulatory arrest (CA); 75%, responses after 11–12 minutes of supine leg exercise at 75% maximum VO$_2$; 75%+CA, responses after 9 minutes of supine leg exercise at 75% maximum VO$_2$ followed by 45 seconds to 2 minutes of CA. It can be seen that each successive intervention tends to shift downward the forearm conductance at any given time point. Thirty seconds of data collection was obtained for all subjects for all interventions. In six of seven subjects, data were obtained at 45 seconds for 75%+CA; at 90 seconds, data were obtained in six of seven subjects for 75% and in four of seven during 75%+CA.
the higher workload led to a lower forearm conductance than noted during circulatory arrest after the 25% workload. 4) LBNP to −40 mm Hg did not alter peak forearm blood flow or vascular conductance.

We believe these observations suggest that metaboreceptor-mediated responses during exercise are capable of vasoconstricting maximally dilated vascular beds. The magnitude of the vasoconstriction depends on the level of exercise (25%+CA vs. 75%+CA). Moreover, we suggest that during the exercise without leg circulatory arrest some activity-related influence acts to oppose metaboreceptor-induced vasoconstriction to active skeletal muscle. Finally, our data would suggest that baroreceptor unloading is incapable of causing the degree of vasoconstriction noted during the supine exercise studies.

The possibility that metaboreceptor stimulation may be responsible for the sympathetically mediated constriction that opposes metabolic vasodilation has recently been suggested by Rowell and Sheriff.6 We believe that the findings of the present report are the first in human subjects to confirm this hypothesis. Our finding that metaboreceptor stimulation is workload dependent is consistent with recent human studies in which muscle sympathetic nerve activity in the peroneal nerve increased as the level of upper body arm crank exercise increased15 and studies in which the increase in calf vascular resistance in response to static forearm exercise was also dependent on the amount of exercise.13 The present findings expand on these studies by examining the ability of different degrees of metaboreceptor stimulation to regulate peak blood flow delivery to metabolically active skeletal muscle.

Interactions Between Metaboreceptors and Central Neural Influences

Our results do not support the concept that central command increases sympathetic outflow during exercise.20,21 This is not to imply that central command cannot increase sympathetic outflow under certain experimental conditions but, rather, to suggest that during exercise, when all systems are intact, some central volitional influence actually acts to oppose metaboreceptor-mediated forearm vasoconstriction. This observation is consistent with the contention of Mark et al23 that central volitional influences act to oppose metaboreceptor-mediated increments in sympathetic nerve traffic. In addition, our findings could also be explained by a central process that causes a cholinergic forearm vasodilation during leg exercise that is not present during the periods of circulatory arrest after leg exercise. However, the magnitude of the differences in blood flow between the two conditions (exercise and exercise followed by circulatory arrest) is larger than has been previously described for cholinergically mediated vasodilation in humans.24 Further studies will be necessary to clarify these potential explanations.

Our results are also at odds with those of Rowell et al,25 who used leg exercise (100–150 W) after circulatory arrest as a maneuver to alter resting forearm blood flow. In this previous study, a forearm vasodilation was observed during leg occlusion in four of five subjects. These authors suggested that the increments in forearm flow were mediated by a large baroreflex drive that opposed the metaboreflex-mediated rise in blood pressure. Much of the difference in results between these two studies may stem from the fact that in Rowell’s report a skin vasodilation to dissipate heat may have overshadowed any changes in blood flow in the metabolically inactive skeletal muscle. In our studies, increments in peak skin flow are not likely to overshadow changes in muscle flow since changes in muscle flow are very substantial and represent the major contributor to the peak reactive hyperemic blood flow response.9 In addition, our 75%+CA protocol may have caused a greater degree of leg metaboreceptor stimulation than noted in the Rowell et al study (approximately 170 W in our study vs. 100–150 W in their previous study).

Our study was not designed to specifically address the role of baroreceptors in regulating vascular conductance during exercise. However, at each workload leg circulatory arrest had no effect on MAP, yet leg circulatory arrest was associated with a reduction in maximal conductance. This suggests that arterial baroreceptor influences cannot explain the reduction in forearm conductance associated with leg circulatory arrest. Changes in low-pressure baroreceptor tone were not likely to be important since the subjects were performing supine exercise, and it is unlikely that central venous pressure fell substantially during leg circulatory arrest. Furthermore, the studies using LBNP to −40 mm Hg during maximal forearm vascular conductance measurements suggest that enhanced sympathetic tone secondary to changes in baroreceptor activity are incapable of altering peak forearm vascular conductance. This observation is consistent with prior human studies.26,27

Potential Limitations

There are several important issues that must be considered before accepting our results at face value. First, in our paper we are assuming that the vasodilation associated with 10 minutes of circulatory arrest mimics the vasodilation associated with maximal exercise. This is a potential concern since the normalized (ml/min/100 ml tissue) levels of peak blood flow reported with plethysmographic techniques are lower than those reported with thermodilution techniques.4 This difference is likely explained by the fact that the thermodilution technique predominantly measures flow from the quadriceps femoris, a relatively homogeneous mass of skeletal muscle, whereas the strain-gauge method includes flow to tissues with limited vasodilator potential such as skin and bone. In addition, plethysmography measures flow to many skeletal muscles. Because different
skeletal muscles can have very different vasodilation potentials,\(^28\) it is not surprising that plethysmography will yield lower peak flows than those noted with the thermodilution method.

Second, it could be argued that the forearm vasoconstriction seen with leg circulatory arrest is due primarily to the pain of cuff occlusion. This is unlikely since in a group of six individuals leg occlusion alone at the time of the release of 10 minutes of forearm circulatory arrest did not affect peak forearm blood flow. Along similar lines, we cannot exclude that the pain due to ischemia of the large muscle mass during the 75%+CA protocol was an important factor in lowering conductances. This factor could influence our results regarding central command and metaboreceptor stimulation. However, at the time of peak forearm flow measurements, leg occlusion had been in effect only 30 seconds, and the subjects reported that leg discomfort was no worse than during leg exercise alone. Furthermore, MAP during the leg circulatory arrest protocols was not statistically greater than during the comparative levels of exercise. If pain were a major factor, we would have anticipated the blood pressure to be higher during the leg circulatory arrest protocols. Finally, if pain were the critical factor responsible for the reduction in forearm conductance during circulatory arrest at the 75% workload, we would not have anticipated the 20% reduction in conductance associated with the less painful leg circulatory arrest at the 25% workload. Despite the experiments with leg occlusion alone and the above arguments, the potential influences of pain cannot be entirely excluded, and our results regarding central command and metaboreceptors must be viewed in light of this limitation.

The last potential limitation of our data is that to separate the influences of metabolic “dilation” from metabolic constriction it was necessary to generate the constricting stimulus in a different muscle bed (legs) than the muscle beds that were metabolically dilated (forearm). This raises concern because it is possible that sympathetic outflow to the forearm actually overestimates sympathetic responses that occur in the legs during exercise. Wallin et al\(^29\) have recently compared muscle sympathetic nerve traffic with the inactive radial and peroneal nerves of subjects during muscle ischemia after exercise. They found that radial nerve activity increased more than peroneal nerve activity. However, in these studies, the stimulus that increased nerve activity was ischemia after handgrip and not circulatory arrest after leg exercise. As suggested by Wallin et al, this raises the possibility that a portion of the increase in radial nerve sympathetic activity was due to a segmental spinal sympathetic reflex. This clearly could not be the case in the present study. Therefore, we believe that our data support the conclusion that metaboreceptor stimulation strongly opposes metabolic vasodilation in metabolically active beds.

In conclusion, the present report provides evidence that stimulation of the skeletal muscle metaboreflex causes a vasoconstriction capable of significantly limiting extreme peripheral vasodilation. Furthermore, our results are entirely consistent with the concept that metaboreceptor-mediated vasoconstriction is the predominant and crucial mechanism responsible for preventing cardiac output from being outstripped by the massive levels of vasodilation that occur during heavy systemic exercise.

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