Severe exercise alters the strength and mechanisms of the muscle metaboreflex

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Augustyniak, Robert A., Heidi L. Collins, Eric J. Ansorge, Noreen F. Rossi, and Donal S. O’Leary. Severe exercise alters the strength and mechanisms of the muscle metaboreflex. Am J Physiol Heart Circ Physiol 280: H1645–H1652, 2001.—Previous studies have shown that in dogs performing mild to moderate treadmill exercise, partial graded reductions in hindlimb blood flow cause active skeletal muscle to become ischemic and metabolites to accumulate thus evoking the muscle metaboreflex. This leads to a substantial reflex increase in mean arterial pressure (MAP) mediated almost solely via a rise in cardiac output (CO). However, during severe exercise CO is likely near maximal and thus metaboreflex-mediated increases in MAP may be attenuated. We therefore evoked the metaboreflex via partial graded reductions in hindlimb blood flow in seven dogs during mild, moderate, and severe treadmill exercise. During mild and moderate exercise, there was a large rise in CO (1.5 ± 0.2 and 2.2 ± 0.3 l/min, respectively), whereas during severe exercise no significant increase in CO occurred. The rise in CO caused a marked pressor response that was significantly attenuated during severe exercise (26.3 ± 7.0, 33.2 ± 5.6, and 12.2 ± 4.8 mmHg, respectively). We conclude that during severe exercise the metaboreflex pressor response mechanisms are altered such that the ability of this reflex to increase CO is abolished, and reduced pressor response occurs only via peripheral vasoconstriction. This shift in mechanisms likely limits the effectiveness of the metaboreflex to increase blood flow to ischemic active skeletal muscle. Furthermore, because the metaboreflex is a flow-raising reflex and not a pressure-raising reflex, it may be most appropriate to describe the metaboreflex magnitude based on its ability to evoke a rise in CO and not a rise in MAP.

arterial pressure (MAP), ventricular performance, central blood volume mobilization, and vasoconstriction in the renal and nonischemic active skeletal muscle vasculatures (1, 7, 8, 12, 13, 15, 17–20, 25, 30, 32, 37). Previous studies have shown that during mild to moderate workloads this pressor response is primarily due to increased CO (4, 7, 18, 30, 37). Augmentation of CO increases the total amount of blood available for organ perfusion and thus provides an important contribution toward improving the ischemic conditions that can occur within active skeletal muscle. Because there is a marked increase in CO with metaboreflex activation at these workloads and little net change in the level of total vascular conductance (TVC) in all nonischemic areas (7, 30, 37), the rise in perfusion pressure with metaboreflex activation is a consequence of the substantial increase in CO. This is of fundamental importance because the metaboreflex is most often viewed as a flow-sensitive, flow-raising reflex and not a pressure-sensitive, pressure-raising reflex (23, 26, 28). Substantially raising perfusion pressure without any increase in CO during heavier exercise would likely not markedly improve skeletal muscle BF. In this setting, >85% of CO (14) is directed toward active skeletal muscle, and a substantial pressor response via peripheral vasoconstriction could only occur by vasoconstricting this vascular bed (16, 21, 26).

The role of the metaboreflex during severe exercise has never been investigated. Rowell and colleagues (5, 24, 26) have suggested that the metaboreflex may actually become more powerful during severe exercise because the strength of the metaboreflex is a function of active muscle mass, and severe exercise presumably requires more active muscle than lower exercise intensities. Alternatively, the ability of the metaboreflex to increase BF to ischemic active skeletal muscle during severe exercise may become limited in that CO is likely already at or near-maximal levels, and any significant elevation in MAP could only occur via vasoconstriction of skeletal muscle (which would seem counterproductive). Therefore, a pressor response resulting from skeletal muscle ischemia during severe exercise may

Afferent Neurons located within active skeletal muscle are stimulated when the metabolic byproducts of muscle metabolism accumulate due to a mismatch between skeletal muscle blood flow (BF) and metabolism. This elicits a reflex increase in effenter sympathetic nerve activity and a powerful pressor response termed the muscle metaboreflex. Activation of the metaboreflex during mild to moderate exercise evokes marked increases in heart rate (HR), cardiac output (CO), mean arterial pressure (MAP), ventricular performance, central blood volume mobilization, and vasoconstriction in the renal and nonischemic active skeletal muscle vasculatures (1, 7, 8, 12, 13, 15, 17–20, 25, 30, 32, 37). Previous studies have shown that during mild to moderate workloads this pressor response is primarily due to increased CO (4, 7, 18, 30, 37). Augmentation of CO increases the total amount of blood available for organ perfusion and thus provides an important contribution toward improving the ischemic conditions that can occur within active skeletal muscle. Because there is a marked increase in CO with metaboreflex activation at these workloads and little net change in the level of total vascular conductance (TVC) in all nonischemic areas (7, 30, 37), the rise in perfusion pressure with metaboreflex activation is a consequence of the substantial increase in CO. This is of fundamental importance because the metaboreflex is most often viewed as a flow-sensitive, flow-raising reflex and not a pressure-sensitive, pressure-raising reflex (23, 26, 28). Substantially raising perfusion pressure without any increase in CO during heavier exercise would likely not markedly improve skeletal muscle BF. In this setting, >85% of CO (14) is directed toward active skeletal muscle, and a substantial pressor response via peripheral vasoconstriction could only occur by vasoconstricting this vascular bed (16, 21, 26).

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be attenuated compared with that during mild or moderate exercise. The present study was designed to investigate whether the metaboreflex-mediated pressor response during severe exercise is reduced compared with that during mild and moderate exercise and whether the mechanisms mediating this reflex pressor response are altered.

**METHODS**

All experiments were performed using seven conscious dogs of either gender (weight 21–26 kg) selected for their willingness to run on a motor-driven treadmill. All procedures were reviewed and approved by the Institutional Animal Care Committee and conformed to National Institutes of Health guidelines.

**Surgical preparation.** The animals were prepared in a series of three sterile surgical sessions with at least 1 wk between surgeries and between the last surgery and the first experiment, as previously described in detail (2, 7, 18, 19). For all procedures anesthesia was induced with Pentothal Sodium and maintained with isoflurane. Cefazolin (500 mg iv) was administered both pre- and postoperatively and then cephalxin (30 mg/kg by mouth, 2 times/day) was given to avoid infection. During recovery from surgery, buprenorphine (0.015 mg/kg iv) and acepromazine (0.1 mg/kg im) were administered for analgesia and sedation whenever deemed necessary.

In the first procedure, through a right (n = 6) or left (n = 1) thoracotomy at the fourth intercostal space, a 20-mm BF transducer (Transonic Systems) was placed around the ascending aorta to monitor CO. For unrelated studies, in all animals stainless steel electrodes were sutured to the apex of the left ventricle (for ventricular pacing) and in one animal a 3-mm BF transducer (Transonic Systems) was placed around the left circumflex artery and two ultrasonic dimension crystals (Sonometrics) were sutured into the epicardium of the left ventricle just below the surface of the heart. The pericardium was reapproximated and the chest was closed in layers.

In the second procedure, via a midline laprotomy, BF transducers (Transonic Systems) were placed around the terminal aorta (10 mm) and the left renal artery (4 mm) to monitor hindlimb BF (HLBF) and renal BF (RBF), respectively. A 10-mm vascular occluder (In Vivo Metrics) was placed around the terminal aorta just distal to the HLBF probe. All side branches between the iliac arteries and the HLBF probe were ligated and severed. A catheter was placed in a side branch of the aorta proximal to the HLBF probe and occluder to monitor MAP.

In a final procedure, a catheter was inserted into the jugular vein and advanced to the atrial-caval junction to monitor central venous pressure (CVP). In three animals arterial and venous catheters were inserted into small side branches of the femoral artery and vein to monitor femoral arterial pressure (FAP) and inject drugs unrelated to the present investigation, respectively. In three additional animals for unrelated studies, a 4-mm vascular occluder (In Vivo Metrics) was placed around each common carotid artery. All cables, wires, occluder tubings, and catheters were tunneled subcutaneously and exteriorized between the scapulae.

**Experimental procedures.** All experiments were performed after the animals had fully recovered from surgery and were active, afebrile, and of good appetite. Each animal was brought to the laboratory and allowed to roam freely for 15–30 min. The dog was then directed to the treadmill and the BF transducers were connected to the flowmeters (Transonic Systems). The MAP and CVP catheters were connected to pressure transducers (Transpac IV, Abbott Laboratories). HR was monitored via a cardiograph triggered by the CO signal. All data were sampled by a laboratory computer at 1,000 Hz and mean values for each cardiac cycle were saved on hard disk for subsequent analysis.

The muscle metaboreflex was activated during mild (3.2 km/h, 0% grade), moderate (6.4 km/h, 10% grade), and severe (8.0 km/h, 20% grade) exercise intensities. Occasionally two experiments were performed on the same dog with ~30 min between each run. The treadmill was started and after 3–5 min all data reached steady state. Thereafter, the hindlimb occluder was partially inflated such that hindlimb perfusion was progressively reduced. Each level of reduction in hindlimb perfusion was maintained until all variables reached steady state (3–5 min).

**Data and statistical analysis.** One-minute averages of all variables were taken during steady-state exercise and at each level of partial vascular occlusion. RBF was multiplied by two to account for blood directed toward both kidneys. Renal vascular conductance (RVC) was calculated as [RBF/(MAP - CVP)]. Conductance directed everywhere besides the hindlimbs and kidneys (EVC) was calculated as [CO - (HLBF + RBF)/(MAP - CVP)]. TVC and hindlimb vascular conductance (HLVC) were calculated as [CO/(MAP - CVP)] and [HLBF/(MAP - CVP)], respectively. The data were analyzed as first described by Wyss and colleagues (37). During mild exercise initial reductions in hindlimb perfusion did not evoke metaboreflex responses. However, once HLBF is reduced below an apparent threshold level, there are large increases in MAP, CO, and HR. Thus the relationship between HLBF and the efferent mechanisms of this reflex during mild exercise is “dogleg” shape. The data were therefore approximated by two intersecting regression lines: an initial response line that includes free-flow exercise and each level of partial vascular occlusion that did not evoke metaboreflex responses. However, once HLBF is reduced below an apparent threshold level, there are large increases in MAP, CO, and HR. Thus the relationship between HLBF and the efferent mechanisms of this reflex during mild exercise is “dogleg” shape. The data were therefore approximated by two linear regression lines: an initial response line that includes free-flow exercise and each level of partial vascular occlusion that did not evoke metaboreflex responses. However, once HLBF is reduced below an apparent threshold level, there are large increases in MAP, CO, and HR. Thus the relationship between HLBF and the efferent mechanisms of this reflex during mild exercise is “dogleg” shape. 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way ANOVA for repeated measures was used to compare the hemodynamic values at rest versus free-flow exercise (see Table 1) and the strength (gain) of metaboreflex control of MAP, CO, HR, EVC, and RVC between workloads. The gains were calculated as the respective variable (MAP, mmHg; CO, l/min; HR, beats/min; and EVC and RVC, ml/min−1·mmHg−1) divided by HLBF measured in l/min (e.g., the slope of the relationship of the response vs. HLBF; see Figs. 2 and 3). When ANOVA indicated significance, individual means were compared with a C-matrix test for simple effects using Systat 8.0. In addition, the gains of each response were compared with zero by using a dependent t-test. At each workload the free-flow level of each variable was compared to that observed with maximal metaboreflex activity via the muscle metaboreflex. Responses during severe exercise there were substantial increases in CO with metaboreflex activation, which resulted in a large pressor response (no reduction in EVC occurred, indicating no net peripheral vasconstriction). However, during severe exercise CO was unchanged (P = 0.122), whereas EVC decreased significantly (P = 0.032) with hindlimb ischemia, which led to a pressor response that was significantly attenuated compared with mild and moderate exercise. In addition, note the large reductions in RBF with metaboreflex activation during severe exercise. Although CVP rose markedly as exercise intensity increased, there was no significant rise between free-flow exercise and maximal metaboreflex activation during any of the workloads.

Figure 3 shows the individual gains for metaboreflex control of MAPactive, CO, HR, EVC, and RVC. The gains for MAPactive decreased as exercise intensity increased. The gains for CO and HR were quite substantial during mild and moderate exercise; however, both were greatly reduced during severe exercise. In fact the gain of CO during severe exercise was not significantly different from zero (P = 0.115). The gains for EVC during mild and moderate exercise were not significantly different from zero, whereas the EVC gain during severe exercise was significantly different from zero and from that during mild exercise. The gains for

Table 1. Mean hemodynamic data at standing rest and during free-flow exercise at each workload

<table>
<thead>
<tr>
<th>Workload</th>
<th>MAP, mmHg</th>
<th>CO, l/min</th>
<th>HR, beats/min</th>
<th>TVC, ml/min−1·mmHg−1</th>
<th>EVC, ml/min−1·mmHg−1</th>
<th>CVP, mmHg</th>
<th>RBF, ml/min</th>
<th>HLBF, l/min</th>
<th>HLVC, l/min−1·mmHg−1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>97.6 ± 2.2</td>
<td>3.7 ± 0.1</td>
<td>87.1 ± 3.6</td>
<td>40.5 ± 1.7</td>
<td>30.3 ± 1.3</td>
<td>1.7 ± 0.3</td>
<td>217.3 ± 18.6</td>
<td>0.7 ± 0.0</td>
<td>7.5 ± 0.5</td>
</tr>
<tr>
<td>3.2 km/h</td>
<td>99.8 ± 4.1</td>
<td>5.7 ± 0.3*</td>
<td>122.3 ± 5.2</td>
<td>43.0 ± 3.1*</td>
<td>64.1 ± 6.2*</td>
<td>2.8 ± 0.9</td>
<td>201.8 ± 34.0</td>
<td>1.5 ± 0.1*</td>
<td>15.7 ± 2.1*</td>
</tr>
<tr>
<td>6.4 km/h, 10% Grade</td>
<td>109.3 ± 6.6†</td>
<td>9.7 ± 0.5†</td>
<td>194.3 ± 7.1†</td>
<td>59.6 ± 4.6*</td>
<td>415.2 ± 9.4†</td>
<td>5.4 ± 1.3†</td>
<td>220.0 ± 37.0</td>
<td>3.1 ± 0.3†</td>
<td>30.9 ± 4.3†</td>
</tr>
<tr>
<td>8.0 km/h, 20% Grade</td>
<td>136.4 ± 5.8†</td>
<td>14.8 ± 0.8†</td>
<td>260.7 ± 8.2†</td>
<td>115.6 ± 9.4†</td>
<td>80.8 ± 7.1†</td>
<td>10.4 ± 1.3†</td>
<td>177.6 ± 29.9†</td>
<td>4.9 ± 0.3†</td>
<td>39.1 ± 3.4†</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; TVC, total vascular conductance; EVC, vascular conductance to all areas except hindlimbs and kidneys; CVP, central venous pressure; RBF, renal blood flow; RVC, renal vascular conductance; HLBF, hindlimb blood flow; HLVC, hindlimb vascular conductance; *P < 0.05 vs. rest; †P < 0.05 vs. previous workload.
RVC during moderate and severe exercise were significantly reduced compared with that during mild exercise; however, they were not different from each other.

**DISCUSSION**

The major new finding in this study was that the strength and mechanisms of the muscle metaboreflex are markedly altered during severe exercise. In this setting, the metaboreflex-mediated rise in CO was abolished, which led to differential strengths and mechanisms of the metaboreflex pressor response when compared across workloads. The reduced ability of the metaboreflex to increase CO during severe exercise likely limits the effectiveness of this reflex to increase BF to ischemic active skeletal muscle.

**Workload alters the mechanisms of the metaboreflex pressor response.** Several studies have demonstrated that hindlimb ischemia in conscious dogs performing mild to moderate exercise evokes marked increases in HR, ventricular performance, and central blood volume mobilization, which results in a pressor response that is mediated primarily via an increase in CO because there is little net peripheral vasoconstriction (4, 7, 17–19, 30, 37). Similar results were obtained during mild and moderate exercise in our current study. The ability to increase CO is likely crucial, in that the most potentially beneficial way the metaboreflex could increase BF to the ischemic muscle and reduce the metabolic stimulus is to increase the total amount of BF available for organ perfusion. However, as exercise intensity rises toward very heavy workloads, CO may be at or near maximum and the ability of the metaboreflex to elicit further increases in CO may become limited. The functional significance of the metaboreflex during severe exercise has not been previously investigated; however, two recent studies from our laboratory have investigated the role of this reflex in situations where increases in CO were experimentally or pathophysiologically constrained and the metaboreflex-induced pressor responses were attenuated. Metaboreflex activation in dogs during mild exercise with constant HR (ventricular pacing) and β-adrenergic blockade (30) or in dogs with heart failure during mild and moderate exercise (7) resulted in significantly smaller pressor responses that were mediated solely via peripheral vasoconstriction. This response pattern is remarkably similar to what occurred in the current study during severe exercise in normal dogs where there was a reduced pressor response, no rise in CO, and an increase in peripheral vasoconstriction. Thus the magnitude of a metaboreflex pressor response appears to be dependent on the ability to increase CO. If skeletal muscle ischemia occurs when there is sufficient cardiac reserve (i.e., mild or moderate exercise), the metaboreflex will first increase the total amount of BF available, e.g., increase CO. However, when the cardiac reserve is depleted or impaired, the metaboreflex reverts to peripheral vasoconstriction in an apparent attempt to redistribute as much BF as possible away from vascular beds where it is not absolutely necessary toward the ischemic skeletal muscle. This complete reversal in the mechanisms of the pressor response from mild to severe exercise points to the flow-seeking properties of this reflex.

What vascular beds vasoconstrict and cause the pressor response during severe exercise? Clearly there is significant vasoconstriction within the kidneys with metaboreflex activation during all three exercise intensities. However, is this renal vasoconstriction sympathetically mediated, or is it the result of an autoregulatory or humoral response? Using a preparation similar to that used in the present study, Mittelstadt and colleagues (13) observed metaboreflex-mediated changes in RBF and RVC and found that the decrease in RVC was not affected by sympathetic denervation. Inasmuch as no consistent change in RBF occurred in
either innervated or denervated kidneys, they concluded that this metaboreflex-induced renal vasoconstriction was due to either an autoregulatory response to the increase in arterial pressure or circulating vasoactive substances (possibly catecholamines eliciting enhanced vasoconstriction in the denervated kidney due to denervation supersensitivity). They also concluded that this reflex does not reduce RBF and proposed that because no change in RBF occurred in their study, the marked reductions in RBF seen during strenuous exercise in dogs with reduced ability to increase CO and/or oxygen delivery [e.g., heart failure, anemia, splenectomy, or atrioventricular block (9, 11, 34–36)] are not due to metaboreflex activation. However, it is important to note that in the study by Mittelstadt and co-workers (13) the metaboreflex responses to only relatively mild exercise were investigated (a workload wherein a clear metaboreflex threshold was apparent). The RBF and RVC responses observed in the present study during the lowest workload were quite similar to those observed by Mittelstadt and co-workers (13); however, in contrast, during moderate and severe exercise significant reductions in both RBF and RVC occurred with imposed reductions in HLBF. Because significant and often marked decreases in RBF were observed with hindlimb ischemia at the higher workloads (~50% reduction in RBF during severe exercise, see Fig. 2), this vasoconstriction is unlikely due solely to autoregulation. In addition, a recent study from our laboratory (7) concluded that in dogs with heart failure a portion of the renal vasoconstriction seen during moderate exercise may be due to tonic metaboreflex activation inasmuch as the HLBF level observed before any imposed reductions was already below the metaboreflex threshold observed in the same animals before induction of heart failure. Because during moderate workloads often no metaboreflex threshold was seen (and was never observed during severe exercise), this reflex may become active as workload increases and thus the decrease in RBF and RVC seen in the present study during free-flow exercise at the highest workload may stem from tonic metaboreflex activation. However, we do not want to imply that this renal vasoconstrictor response is important in blood pressure regulation per se (it accounts for only ~1 mmHg of the pressor response), but that it may serve as an indicator of the intense sympathetic activation that likely occurs. This could function to redirect BF away from inactive regions and toward ischemic regions, albeit the total magnitude of this redistribution is small because the vast majority of CO (~85%) is already directed to the active skeletal muscle during maximal exercise.

Active skeletal muscle may be another potential target of the increased sympathetic outflow that resulted from metaboreflex activation, as suggested by Rowell and colleagues (26, 28, 33). Mittelstat and co-workers (12) have shown that metaboreflex activation during moderate exercise causes vasoconstriction within nonischemic active skeletal muscle of the forelimbs of dy-
namically exercising dogs. In addition, during severe exercise most of CO and thus vascular conductance is directed toward active muscle and if CO is at maximal levels, a large pressor response could likely only occur via vasoconstriction of active muscle (16). However, utilizing measurements of the distribution of CO via microspheres in resting dogs from Hales and Dampney (6) and during near-maximal exercise from Musch and co-workers (14), we calculate that the small pressor response observed with metaboreflex activation during severe exercise (12 mmHg) could be due to vasoconstriction in inactive areas if these vascular beds vasoconstricted by ~75%. Although we do know that the metaboreflex-mediated pressor response during severe exercise was mediated via peripheral vasoconstriction, we are unable to distinguish whether or not at least part of the pressor response resulted from increased vasoconstrictor tone to active muscle or to inactive vascular beds.

What hemodynamic variable best describes the strength (gain) of the metaboreflex? Sagawa (29) defined open-loop gain as the ratio of the magnitude of a steady-state response to the magnitude of a steady-state stimulus. Using virtually the same preparation that was used in the present study, Wyss and colleagues (37) were the first to estimate the open-loop gain for metaboreflex control of MAP by dividing increases in MAP by the reductions in femoral perfusion pressure that were due to partial occlusion of the terminal aorta; this resulted in a traditional unitless gain. Most recent calculations have estimated the open-loop gain of metaboreflex control of MAP to be approximately ~3 (17, 19, 31), meaning that when activated, the muscle metaboreflex increases MAP by 3 mmHg for every 1 mmHg reduction in hindlimb perfusion pressure. All studies in dogs that have calculated a gain for the metaboreflex have utilized mild or moderate exercise (17, 19, 31, 32, 37), which are workloads where CO is the primary mediator of the pressor response (7, 30, 37). Because the metaboreflex is believed to be a flow-raising reflex, we propose that the ability to increase CO may more accurately describe the functional importance of this reflex. We estimated open-loop gain of metaboreflex control of CO as ~3.3 (via the slope of the CO-HLBF relationship; see Fig. 2) during mild and moderate exercise. This compares quite well to what Sheriff and colleagues (31) and O’Leary (17) have reported (~2.9 and ~3.2, respectively) especially given that the calculations are fundamentally different. O’Leary and Sheriff (22) estimated the ability of the metaboreflex to restore BF to ischemic active skeletal muscle (closed-loop gain), and found that metaboreflex activation in dogs during mild and moderate exercise induced a pressor response that restored ~50% of the flow deficit induced by partial vascular occlusion. It is controversial whether or not this occurs in humans (10, 27). The open-loop gain of ~3.3 that we calculated during mild and moderate exercise corresponds to a closed-loop gain of ~0.77, meaning that the metaboreflex can correct a deficit in skeletal muscle BF by 77%. Previous reports for the closed-loop gain of the metaboreflex vary between ~0.50 and ~0.75 (22) during mild to moderate workloads (31). During severe exercise the metaboreflex gain for control of CO was abolished and the gain of the pressor response was markedly attenuated suggesting that the inability to increase CO limited the amount of BF available to alleviate the skeletal muscle ischemia within the hindlimb. Therefore utilizing the CO gain to describe the strength of the metaboreflex may be more appropriate than using the MAP gain, as the primary objective of this reflex is presumably to increase BF to ischemic muscle, and under conditions where BF cannot significantly increase the function of this reflex may become limited.

Limitations of gain calculations. Estimating the metaboreflex gain using the MAP-FAP or CO-HLBF relationships is not a perfect method. A problem with using the MAP-FAP relationship to estimate a gain is that the metaboreflex is commonly activated by mechanically reducing BF directed toward a bed of skeletal muscle with the use of vascular occluders, pressure cuffs, or positive pressure (1, 3, 10, 27, 37). Vascular occlusion causes a reduction in vascular conductance which can cause MAP to rise, therefore, the stimulus used to activate this reflex also contributes to the pressor response. In the current study we isolated the active rise in MAP evoked by metaboreflex activation [as first described by Wyss and colleagues (37)] by subtracting the passive rise in MAP at each level of reduction in hindlimb perfusion (e.g., that predicted to occur mechanically due to partial occlusion) from the observed MAP. One caveat of this calculation is that the passive rise in MAP results from the reduction in HLVC due to inflation of the vascular occluder, as well as from changes within the hindlimb vasculature itself. Three animals in our study were instrumented with femoral arterial catheters, allowing us to calculate the changes in vascular resistance that resulted from the vascular occluder [(MAP – FAP)/HLBF] and from active changes within the hindlimb vasculature [(FAP – CVP)/HLBF]. During mild exercise there was an ~13% increase in resistance within the hindlimb vasculature, during moderate exercise there was no change, and during severe exercise there was an ~7% decrease in hindlimb vascular resistance. Thus during mild exercise a small portion of the passive rise in MAP was due to an increase in hindlimb vascular resistance and not the occluder. In contrast, during severe exercise the passive rise in MAP that resulted from vascular occlusion is somewhat underestimated because the hindlimb vasculature dilated slightly.

There is also an inherent problem with using the CO-HLBF relationship to estimate gain, because this assumes that all of the increase in CO is directed toward the ischemic muscle, which is likely invalid. We do know that BF to nonactive vascular beds such as the kidneys does not increase with metaboreflex activation during mild exercise and decreases at heavier workloads, and it is possible that this occurs in other nonactive beds such as the splanchnic organs (7, 13, 30). However, in the study by Mittelstat and co-workers...
Muscle metaboreflex during severe exercise

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(12), whereas metaboreflex activation did cause a decrease in vascular conductance within the forelimbs, the vasoconstrictor response was disproportionate to the pressor response and forelimb BF increased slightly. Thus some of the increased CO with metaboreflex activation is directed to nonischemic active skeletal muscle. Furthermore, with the metaboreflex-induced increases in HR and CO in addition to increased ventricular afterload (MAP) and likely myocardial contractility (18), there will presumably be an increase in myocardial oxygen demand. It is therefore probable that a significant fraction of the metaboreflex-mediated increase in CO may be directed to the heart itself, as discussed by Sheriff and colleagues (30). Clearly neither gain calculation is perfect, and the caveats of each calculation may account for some of the variation that has been reported for estimations of metaboreflex closed-loop gain.

In summary, the mechanisms of the metaboreflex pressor response were different across workloads. During mild and moderate exercise the pressor responses were the result of substantial increases in CO. In contrast, during severe exercise no significant further increase in CO during severe exercise was the result of substantial increases in CO. In mild and moderate exercise the pressor responses were the result of substantial increases in CO. In severe exercise no significant further increase in CO during severe exercise were the result of substantial increases in CO. In

References


