Muscle metaboreflex control of cardiac output and peripheral vasoconstriction exhibit different latencies

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Augustyniak, Robert A., Eric J. Anzorge, and Donal S. O'Leary. Muscle metaboreflex control of cardiac output and peripheral vasoconstriction exhibit different latencies. Am. J. Physiol. Heart Circ. Physiol. 278: H530–H537, 2000.—Experiments were designed to determine 1) the mechanisms mediating metaboreflex-induced increases in systemic arterial pressure (SAP) in response to total vascular occlusion of hindlimb blood flow [e.g., increases in cardiac output (CO) vs. peripheral vasoconstriction] and 2) whether the individual mechanisms display differential latencies for the onset of the responses. Responses were observed in seven dogs performing steady-state treadmill exercise of mild and moderate workloads (3.2 km/h at 0% grade and 6.4 km/h at 10% grade). Differential latencies were exhibited among CO, nonischemic vascular conductance (NIVC; conductance to all nonischemic vascular beds), and renal vascular conductance (RVC), with peripheral vasoconstriction significantly preceding metaboreflex-mediated increases in CO. In addition, the latencies for SAP were not different from those for NIVC or RVC at either workload. During the lower workload there were small increases and then subsequent decreases in CO before the metaboreflex-induced increase in CO, which did contribute somewhat to the initial increases in SAP. However, the increases in CO mediated by the metaboreflex occurred significantly later than the initial increases in SAP. Therefore, we conclude that the substantial metaboreflex-mediated pressor responses that occur during the initial phase of total vascular occlusion during mild and moderate exercise are primarily caused by peripheral vasoconstriction.

WHEN OXYGEN DELIVERY to active skeletal muscle is insufficient to meet metabolic demands, metabolite concentrations increase and stimulate metabolically sensitive group III and IV afferent nerve endings within the active muscle, eliciting a reflex increase in efferent sympathetic nerve activity and systemic arterial pressure (SAP) termed the muscle metaboreflex. Recently, Sheriff (20) investigated the length of time to the onset of the pressor response induced by total vascular occlusion of the terminal aorta in dogs performing treadmill exercise from mild to moderate workloads. Completely restricting blood flow to the active skeletal muscle of the hindlimbs evoked a substantial pressor response with a latency that was inversely related to workload and markedly shorter than the latency to increments in sympathetic nerve activity attributed to metaboreflex activation previously reported during static muscle contractions (7, 18, 19). However, only SAP was recorded in that study. Inasmuch as SAP is affected by changes in cardiac output (CO) and peripheral vasoconstriction, that study did not distinguish the mechanism of the pressor response or determine whether differential latencies exist among the efferent mechanisms of this reflex.

To our knowledge, the recent investigation by Sheriff (20) is the only study that has examined the latency of the metaboreflex during whole body dynamic exercise. However, several investigators have examined the mechanisms that mediate the metaboreflex-induced pressor response during dynamic exercise. In dogs, it is known that during mild dynamic exercise, graded partial reductions in active skeletal muscle perfusion induce substantial increases in both SAP and CO but cause only minor changes in total vascular conductance (TVC) (14, 21, 31). Relatively small changes in TVC indicate that little net peripheral vasoconstriction is occurring, although there is strong evidence that vasoconstriction does occur in nonischemic vascular beds such as the skeletal muscle of the forelimbs and kidneys (11, 12, 21). In contrast, several studies have shown that in situations in which CO does not or cannot increase, peripheral vasoconstriction can induce a pressor response of similar magnitude. In dogs performing mild dynamic exercise during constant heart rate (ventricular pacing) and β1-adrenergic blockade, metaboreflex activation via graded partial reduction of hindlimb blood flow, as described above, evokes a pronounced increase in SAP that is entirely mediated via peripheral vasoconstriction, inasmuch as CO remained unchanged (21). Moreover, complete thigh occlusion in humans performing dynamic leg exercise causes a significant pressor response even though CO decreases slightly (1). In this study (1), humans did perform occlusive leg exercise; however, blood flow to the lower extremities was not measured before occlusion, and examining the latencies of the hemodynamic variables was not an objective. Thus the specific aims of the present study were to determine the mechanisms that mediate the pressor response during total vascular occlusion of active skeletal muscle and whether these mechanisms display differential latencies.
efferent mechanisms demonstrate differential latencies to muscle metaboreflex activation.

Because Asmussen and Nielsen (1) showed that during occlusive leg exercise a significant pressor response occurs, whereas CO is actually reduced slightly, and because an additional study by Toska et al. (26) showed that the immediate reduction in CO that occurs during occlusive leg exercise is primarily the result of a vagally mediated bradycardia, compounded with the short latency of SAP during metaboreflex activation shown by Sheriff (20), we hypothesized that at least the initial pressor response to total vascular occlusion should be mediated via peripheral vasoconstriction, with increases in CO occurring at some time thereafter.

METHODS

All experiments were performed using seven conscious dogs of either gender (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. Each animal was prepared in a series of surgical sessions with at least 1 wk between surgeries and between the last surgery and the first experiment. 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 cephalixin (30 mg/kg by mouth, 2 times/day) was given to prevent postoperative infection. During recovery from surgery, buprenorphine (0.015 mg/kg iv) and acepromazine (0.1 mg/kg im) were administered for analgesia and sedation when necessary.

In the first procedure, through a right thoracotomy at the fourth intercostal space, a blood flow transducer (Transonic Systems) was placed on the ascending aorta to monitor CO. For subsequent ventricular pacing unrelated to the present study, stainless steel electrodes were sutured to the apex of the left ventricle. The pericardium was reapproximated, and the chest was closed in layers.

In the second procedure, through either a midventral abdominal or retroperitoneal approach, blood flow transducers (Transonic Systems) were placed on the terminal aorta and the left renal artery to monitor terminal aortic (TAQ) and renal blood flow (RBF), respectively. A vascular occluder (In Vivo Metrics) was placed on the terminal aorta just distal to the flow probe. All side branches between the iliac arteries and the flow probe were ligated and severed. A catheter was placed in a side branch of the aorta proximal to the flow probe and occluder to monitor SAP.

In a third procedure, through an axillary incision, a blood flow transducer (Transonic Systems) was placed on the right axillary artery to monitor forelimb blood flow (FLBF).

In a final procedure, arterial and venous catheters were implanted into small side branches of the femoral artery and vein to monitor femoral arterial pressure (FAP) and for infusion of drugs for studies unrelated to the present investigation, respectively. An additional catheter was inserted into the jugular vein and advanced to the atrial-caval junction to monitor central venous pressure (CVP). All flow probe cables, ventricular pacing leads, occluder tubing, 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. The animal was brought to the laboratory and allowed to roam freely for 15–30 min. The animal was then directed to the treadmill, and the blood flow transducers were connected to the flowmeters (Transonic Systems). The FAP, SAP, and CVP catheters were connected to pressure transducers (Transpac IV, Abbott Laboratories). Heart rate (HR) was monitored via a cardiotachometer 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 a hard disk for subsequent analysis.

The muscle metaboreflex was activated during mild (3.2 km/h, 0% grade) and moderate (6.4 km/h, 10% grade) exercise intensities. The treadmill was started, and, after 3–5 min, steady-state levels of each of the output variables were achieved. Thereafter, the hindlimb occluder was rapidly inflated and TAQ decreased to zero within 2–3 s. While the animal continued to run, the occlusion was maintained for 1–1.5 min depending on the exercise intensity. The occluder was then released, the treadmill was shut off, and the animal was allowed to recover for a minimum of 30 min before a second experiment was performed. There were never more than two experiments attempted on the same day.

Data analysis. The vascular conductances through the forelimb or kidney were calculated as FLBF or RBF divided by (SAP – CVP), respectively. Changes in RVC are presented as a percentage of the change from the average control level. Although the trend and latency for RVC are very similar across all dogs included in this study, there was some variability in the absolute RBF values. In three dogs RBF ranged from 61.1 to 87.1 ml/min; however, in three other dogs RBF was substantially higher (108.6 to 161.8 ml/min). TVC was calculated as CO/(SAP – CVP). Nonischemic vascular conductance (NIVC) was calculated as (CO – TAQ)/(SAP – CVP). Subtracting TAQ allows isolation of the systemic responses without interference from the substantial mechanical decrease in TVC that results from occluder inflation. The latency for SAP was analyzed in the manner described by Sheriff (20) and is shown in Fig. 1. Briefly, there was an initial increase in SAP immediately following occluder inflation that was caused by the mechanical effect of terminal aortic occlusion on TVC (8). This was followed by a short stable period, which then led to a second large progressive increase in SAP. The short stable period was averaged, and then a linear regression was performed on arterial pressure versus time through the large rise in SAP. Therefore, the latency was defined as the time period between the occlusion and the point at which the regression line intersects the average of the short stable period. The latencies for CO, HR, and RVC, which were analyzed in the same way, are also shown in Fig. 1. During the first 5–10 s there were rapid changes in each variable, presumably caused by baroreflex activation, followed by a stable period after which substantial increases or decreases occurred depending on the variable. The latencies for these variables were defined as stated above. NIVC responded with an initial increase followed by a relatively steep decrease that occurred 15–20 s postocclusion and continued throughout the remainder of the occlusion.During the same time period in which NIVC reached its highest point and began to decrease, SAP began its very pronounced increase. Therefore, we identified the point at which NIVC began to decrease and defined the latency for this variable as the time period between the occlusion and this point. Finally, although there was a tendency for FLVC to
decrease, especially at the highest exercise intensity, it did not reach statistical significance. Thus we were unable to calculate a latency for this variable. In addition, CVP increased within 4 s during both workloads. Thereafter, during the lower workload it remained unchanged, whereas during the higher workload it continued to increase but at a lower rate. CVP responses did not fit the method of analysis; therefore, the latency for CVP was not calculated.

Monitoring SAP, CO, CVP, and TAQ allows us to isolate how the individual changes in CO and NIVC affect SAP (see discussion of Fig. 5 in DISCUSSION). The individual roles of changes in CO and peripheral vascular conductance were assessed by calculating the predicted level of SAP if NIVC were to remain constant (SAP\textsubscript{CO}, reflecting the cardiac component of the pressor response) or if CO were to remain constant (SAP\textsubscript{NIVC}, reflecting the vasoconstriction component). These were calculated as

\[
\text{SAP}_{\text{CO}} = \left(\frac{\text{CO}_{\text{obs}}}{\text{NIVC}_{\text{avg control}}} + \frac{\text{TVC}_{\text{obs}} - \text{NIVC}_{\text{obs}}}{\text{CVP}_{\text{avg control}}}ight)
\]

\[
\text{SAP}_{\text{NIVC}} = \left(\frac{\text{CO}_{\text{avg control}}}{\text{TVC}_{\text{obs}}} + \frac{\text{NIVC}_{\text{obs}}}{\text{CVP}_{\text{avg control}}}ight)
\]

where the subscripts indicate observed (obs) or average control (avg control) responses. If no change in either CO or NIVC occurred, complete hindlimb occlusion would elicit a large mechanical increase in SAP (SAP\textsubscript{mech}), which was calculated as

\[
\text{SAP}_{\text{mech}} = \left(\frac{\text{CO}_{\text{avg control}}}{\text{NIVC}_{\text{avg control}}} + \frac{\text{TVC}_{\text{obs}} - \text{NIVC}_{\text{obs}}}{\text{CVP}_{\text{avg control}}}ight)
\]

Statistical analysis. A two-way ANOVA for repeated measures was used to compare the latencies at the lower exercise intensity with the corresponding latencies at the higher exercise intensity as well as to compare each of the latencies within a workload. Individual means were compared using the test for simple effect. The software used for all statistical analysis was SYSTAT (version 5.02). An alpha level of P < 0.05 was used to determine statistical significance.

RESULTS

Figure 2 shows the responses to total vascular occlusion of the terminal aorta at the mild exercise intensity, 3.2 km/h at 0% grade. This figure contains averaged data from seven dogs (n = 6 for RVC, n = 5 for FLVC). The latencies for SAP, vascular conductance, and RVC were not statistically different from each other and occurred much earlier than the latencies for CO and HR.

Figure 3 shows the responses to total vascular occlusion of the terminal aorta at the moderate exercise intensity, 6.4 km/h at 10% grade. Figure 3 is based on averaged data from seven dogs (n = 6 for RVC, n = 5 for FLVC). The response patterns of all variables were similar to those during the lower exercise intensity but were larger in magnitude and occurred more rapidly.

Figure 4 shows the latencies for SAP, NIVC, CO, HR, and RVC at both mild and moderate exercise intensities. Each latency at the lower exercise intensity was statistically different (P < 0.05) from the same latency at the higher exercise intensity. As stated earlier, latencies for FLVC and CVP were not calculated.

Table 1 shows the P values calculated when all latencies were compared within each exercise intensity. Note that the latencies for HR and CO were significantly longer than those for SAP, NIVC, and RVC, which were not different from each other.

DISCUSSION

There are two new findings in this study: 1) the efferent mechanisms mediating metaboreflex-induced pressor responses exhibited differential latencies, with vasoconstriction significantly preceding the metabore-
flex-mediated rise in CO, and 2) the first phase of the metaboreflex pressor response seen during total vascular occlusion in dogs during mild and moderate exercise is mediated primarily via peripheral vasoconstriction.

Response patterns and latencies. The patterns of response for all variables at the lower exercise intensity were similar to the corresponding response patterns at the higher exercise intensity. In addition, all latencies were inversely related to exercise intensity. The arterial pressure responses and latencies were very similar to those described by Sheriff (20), who recently investigated the effect of total vascular occlusion of the terminal aorta in dogs performing dynamic exercise of mild to moderate exercise intensities. He found that there was an initial rise in SAP within the first 5 s, followed by a short stable period lasting several seconds. This short, stable period is likely the result of buffering by the arterial baroreflex due to the large decrease in vascular conductance caused by the occlusion (26). This was very well supported by our findings; however, in the study by Sheriff (20), only SAP was monitored. The present data indicate that the effect of a mechanical decrease in vascular conductance does likely evoke baroreflex responses. Specifically, a reflex vasodilation occurred, as indicated by an increased TVC, although RVC did decrease very rapidly, indicating vasoconstriction [likely caused by autoregulation (13)]. However, because the net total effect was vasodilation (increased TVC), other vascular beds must have dilated. In addition, HR and CO were rapidly decreased,

Fig. 2. SAP, vascular conductance (VC), total vascular conductance (TVC), NIVC, CO, HR, RVC, forelimb vascular conductance (FLVC), and central venous pressure (CVP) vs. time in response to complete terminal aortic occlusion during the lower exercise intensity (3.2 km/h, 0% grade). Data are averaged from 7 animals (n = 7 for SAP, VC, CO, and HR; n = 6 for RVC; n = 5 for FLVC). Arrows correspond to onset of response ± SE for each variable. Vertical dashed line represents occluder inflation; horizontal lines from 0 to 80 s represent average control level 1 min before occlusion for each variable. Note that SAP begins to increase at same point that NIVC and RVC begin to decrease.

Fig. 3. SAP, VC, CO, HR, RVC, FLVC, and CVP vs. time in response to complete terminal aortic occlusion during the higher exercise intensity (6.4 km/h, 10% grade). Data are averaged from 7 animals (n = 7 for SAP, VC, CO, and HR; n = 6 for RVC; n = 5 for FLVC). Arrows correspond to onset of response ± SE for each variable. Vertical dashed line represents occluder inflation; horizontal lines from 0 to 60 s represent average control level 1 min before occlusion for each variable. Note that SAP begins to increase at same point that NIVC and RVC begin to decrease.
likely caused by arterial baroreceptor-mediated parasympathetic activation, elicited by the initial rise in SAP as a result of the mechanical effects of total occlusion, as described by Toska et al. (26). After a short latency, TVC then decreased to control levels, indicating significant vasoconstriction, which was evidenced by the rapid rise in SAP. Before the vasoconstriction occurred, HR and CO reversed direction and began to increase back toward control levels. However, this response pattern is likely not caused by the metaboreflex and, importantly, is similar to that seen during rapid forms of baroreflex activation. For example, Strange et al. (25) observed that pulsatile negative pressure applied over the carotid sinus (neck suction) caused rapid reductions in HR that quickly returned toward control level. Using a similar technique but with static pressure, Eckberg (5) found an initial peak (within 2 s) increase in P-P interval, followed by a rapid decrease that reached a stable level that was higher than the control level. Stephenson and Donald (24) found that rapid increases in isolated carotid sinus pressure of conscious dogs resulted in significant rapid initial reductions in HR that rebounded to a steady-state level that was less than the control level. Furthermore, dogs are known to have a strong Bainbridge reflex (2, 3, 6, 27). Therefore, the immediate rise in CVP (stimulating the Bainbridge reflex) during both workloads coupled with the “rebound effect” from the baroreflex are possibilities that may explain the initial rise in HR and CO back toward control levels. Finally, we believe that the initial increases in HR were not mediated via the metaboreflex, inasmuch as the HR then decreased during mild exercise at 24 s. It seems highly unlikely that the metaboreflex would cause HR to increase, then decrease, and then increase again. Therefore, we believe that the metaboreflex-induced latencies for HR and CO occurred during the subsequent rises in both variables, which were significantly longer than the latency for TVC during both workloads. In addition, the latencies for TVC, RVC, and SAP were not different from each other, which indicates that vasoconstriction plays a major role in at least the initial phase of the pressor response. This pattern of metaboreflex activation is in stark contrast to what is observed in graded partial occlusions, in which the pressor response is primarily caused by increases in CO (14, 21, 31).

Potential influences of other cardiovascular reflexes. In the present study hindlimb occlusion caused significant increases in SAP and CVP; therefore, the arterial and cardiopulmonary baroreflexes are likely to be active throughout the entire duration of the occlusion, and previous studies have shown that both of these baroreflexes attenuate muscle metaboreflex pressor responses (4, 16, 22, 30). Interestingly, a recent study by Potts and Mitchell (17) showed that neural input from skeletal muscle afferents resets the threshold of the carotid baroreflex to a higher pressure, which indicates that the extent of arterial baroreceptor buffering of the muscle metaboreflex may wane as muscle afferents become progressively more active. We do not know whether the baroreflexes modulate the latency of the muscle metaboreflex. However, Sheriff et al. (22) showed that the baroreflex does not affect the threshold level of hindlimb perfusion required to activate the muscle metaboreflex during mild exercise; rather, the baroreflex acts to attenuate the magnitude of the pressor response. Similarly, Waldrop and Mitchell (30) demonstrated larger pressor responses to hindlimb ventral root stimulation in anesthetized baroreceptor-denervated cats than in baroreceptor-intact cats. Therefore, we speculate that the baroreflex likely acts to attenuate the rate of increase in SAP, CO, and periphery.

Table 1. P values showing differences between latencies within each exercise intensity

<table>
<thead>
<tr>
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<th>3.2 km/h, 0% Grade</th>
<th>6.4 km/h, 10% Grade</th>
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<tbody>
<tr>
<td>SAP vs. CO</td>
<td>0.002*</td>
<td>0.003*</td>
</tr>
<tr>
<td>SAP vs. NIVC</td>
<td>0.226</td>
<td>0.497</td>
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<tr>
<td>SAP vs. HR</td>
<td>0.000*</td>
<td>0.003*</td>
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<tr>
<td>SAP vs. RVC</td>
<td>0.184</td>
<td>0.215</td>
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<tr>
<td>NIVC vs. CO</td>
<td>0.000*</td>
<td>0.001*</td>
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<tr>
<td>NIVC vs. HR</td>
<td>0.001*</td>
<td>0.002*</td>
</tr>
<tr>
<td>NIVC vs. RVC</td>
<td>0.166</td>
<td>0.286</td>
</tr>
<tr>
<td>HR vs. CO</td>
<td>0.243</td>
<td>0.233</td>
</tr>
<tr>
<td>HR vs. RVC</td>
<td>0.003*</td>
<td>0.009*</td>
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<tr>
<td>RVC vs. CO</td>
<td>0.007*</td>
<td>0.009*</td>
</tr>
</tbody>
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SAP, systolic arterial pressure; CO, cardiac output; NIVC, nonischemic vasculature conductance; HR, heart rate; RVC, renal vascular conductance. *P < 0.05.
eral vasoconstriction without affecting the latency of the responses. However, this has yet to be investigated.

During the latter stages of complete vascular occlusion, the animals often demonstrated substantial fatigue. Thus it is likely that central command increased during the hindlimb occlusion. However, it is unlikely that central command affected the latency of the muscle metaboreflex in these experiments because no obvious signs of fatigue occurred until well after the initiation of the pressor response. Central command could have contributed to the latter stages of the responses to total vascular occlusion. Whereas strong evidence exists that central command can modulate parasympathetic tone, previous studies have shown that central command increases (29), causes no change in (28), or even decreases (10) sympathetic nerve activity. Furthermore, previous studies have shown that lesions of the dorsal lateral sulcus and funiculus (the spinal pathway for metabosensitive afferents) or the intrathecal administration of opiates can abolish the pressor response and tachycardia that normally occur during ischemic exercise (9, 15). These studies provide support for the suggestion that responses to ischemic exercise are mediated via the metaboreflex and not central command.

Mechanisms of the pressor response. Blood pressure can rise through increases in CO and/or peripheral vasoconstriction. Previously, Asmussen and Nielsen (1) demonstrated that the interruption of leg blood flow during exercise on a bicycle ergometer resulted in a significant pressor response that was mediated via peripheral vasoconstriction, inasmuch as CO was reduced slightly. Toska et al. (26) showed that the immediate reduction in HR, and thus CO, that occurred just after the inflation of leg cuffs during leg exercise was eliminated by atropine, albeit a smaller, slower HR decrease still remained. Muscle metaboreflex activation during constant heart rate after β1-adrenergic blockade results in large increases in arterial pressure primarily mediated via peripheral vasoconstriction, whereas before blockade and during the same type of exercise, similar but slightly larger pressor responses occurred mostly because of increases in CO (21). These studies, in concert with that of Sheriff (20), who showed that the latency of the metaboreflex is quite short (as fast as 5 s during moderate exercise), led us to hypothesize that at least the initial pressor response during metaboreflex activation should be mediated via peripheral vasoconstriction.

Figure 5 illustrates the observed pressor response at both exercise intensities (SAPobs) as well as the predicted effects of peripheral vasoconstriction (SAPNIVC), changes in CO (SAPCO), and the mechanical effect of the occluder (SAPmech). During mild and moderate exercise, blood pressure should have risen 28.4 and 47.1 mmHg, respectively, solely because of the mechanical effect of terminal aortic occlusion on TVC. This rise was prevented by a reduction in CO and peripheral vasodilation, presumably mediated via the arterial baroreflex. Once the metaboreflex latency was reached, SAP increased beyond the SAPmech level at 36 and 52 s for mild and moderate workloads, respectively.

The mechanisms that mediate the metaboreflex-induced pressor responses are quite similar between workloads. During the lower workload, as shown in Fig. 5, SAPCO actually rises from the onset of the occlusion until 24 s; however, this increase is somewhat, but not totally, offset by the vasodilation that is indicated by the reduction in SAPNIVC and is also evidenced by the relatively stable level of SAPobs. Immediately after the latency, SAPCO levels off and decreases from 24 to 28 s. This occurs in the same time period during which SAPNIVC is increasing, indicating that the increase in
SAP\textsubscript{obs} is caused by vasoconstriction. Finally, from \textasciitilde 30 to 45 s the rate of rise of SAP\textsubscript{obs} decreases until after 45 s, when the SAP\textsubscript{obs} increases further because of elevations in both SAP\textsubscript{NIVC} and SAP\textsubscript{CO}. During moderate exercise at 6 s, SAP\textsubscript{CO} again rises and SAP\textsubscript{NIVC} drops, maintaining SAP\textsubscript{obs} relatively unchanged from 4 to 10 s. Importantly, after the SAP latency, SAP\textsubscript{CO} stops increasing and remains relatively stable from 12 to 28 s. However, SAP\textsubscript{obs} increases by nearly 25 mmHg, and increasing and remains relatively stable from 12 to 28 s. Importantly, after the SAP latency, SAP\textsubscript{CO} stops elevations in both SAP\textsubscript{NIVC} and SAP\textsubscript{CO}. During moderate to severe exercise at 6 s, SAP\textsubscript{CO} again rises and SAP\textsubscript{NIVC} rises at nearly the same rate during this time period. After \textasciitilde 30 s, rising CO and peripheral vasoconstriction both contribute to the pressor response. Therefore, during both mild and moderate exercise, the initial phase of the metaboreflex-induced pressor response is mediated predominantly via peripheral vasoconstriction.

It is difficult to speculate on the vascular beds in which vasoconstriction occurred in our experiments. Clearly, there was significant vasoconstriction within the kidneys; however, because RVC is only a small fraction of TVC, constriction within this bed does not contribute substantially to the pressor response. In addition, Mittelstadt et al. (11) demonstrated that significant vasoconstriction occurs within the active skeletal muscle of the forelimbs of dynamically exercising dogs during metaboreflex activation via graded partial reductions in hindlimb flow. However, no significant decrease in FLVC was noted during our experiments. The reasons for these confounding results may be that the method of metaboreflex activation was different, or perhaps the latency for constriction within the forelimbs was longer than our animals could run during complete terminal aortic occlusion. In addition, the phasic signal from the forelimb flow probe was highly stance dependent, indicating a large mechanical effect from muscle contraction that may render these data difficult to interpret.

Importance of metaboreflex-mediated peripheral vasoconstriction. Peripheral vasoconstriction is an important mechanism utilized to mobilize blood centrally and maintain or increase CVP, which is crucial in helping to raise CO (18). Figure 3 shows that there is a significant vasoconstriction that occurred from 12 to 20 s. Interestingly, after 14 s, there was a continued rise in CVP throughout the duration of the occlusion that occurred despite an increase in CO. An increase in CO alone with no other compensatory mechanisms should cause CVP to fall because of the inverse relationship that exists between CO and CVP (23). Once beyond its latency there is by definition a significant elevation in CO. In the present study during both workloads, even after CO increased, CVP was either maintained (mild exercise) or increased (moderate exercise). A recent study by Sheriff et al. (21) showed that metaboreflex activation in dogs, via graded partial occlusion, is capable of eliciting substantial central blood volume mobilization. Therefore, the peripheral vascular adjustments mediated by the metaboreflex include those that act to maintain or increase ventricular filling pressure, which is important in the ability to increase CO despite increasing ventricular afterload.

In summary, activation of the muscle metaboreflex via total vascular occlusion in dynamically exercising dogs evokes a substantial pressor response. During both mild and moderate exercise, the initial metaboreflex rise in SAP is predominately mediated via peripheral vasoconstriction. Also, the efferent mechanisms of this reflex exhibit differential latencies.

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