Arterial baroreflex alters strength and mechanisms of muscle metaboreflex during dynamic exercise

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Kim, Jong-Kyung, Javier A. Sala-Mercado, Jaime Rodriguez, Tadeusz J. Scislo, and Donal S. O’Leary. Arterial baroreflex alters strength and mechanisms of muscle metaboreflex during dynamic exercise. Am J Physiol Heart Circ Physiol 288: H1374–H1380, 2005.—Previous studies showed that the arterial baroreflex opposes the pressor response mediated by muscle metaboreflex activation during mild dynamic exercise. However, no studies have investigated the mechanisms contributing to metaboreflex-mediated pressor responses during dynamic exercise after arterial baroreceptor denervation. Therefore, we investigated the contribution of cardiac output (CO) and peripheral vasoconstriction in mediating the pressor response to graded reductions in hindlimb perfusion in conscious, chronically instrumented dogs before and after sinoaortic denervation (SAD) during mild and moderate exercise. In control experiments, the metaboreflex pressor responses were mediated via increases in CO. After SAD, the metaboreflex pressor responses were significantly greater and significantly smaller increases in CO occurred. During control experiments, nonischemic vascular conductance (NIVC) did not change with muscle metaboreflex activation; whereas after SAD NIVC significantly decreased with metaboreflex activation; thus SAD shifted the mechanisms of the muscle metaboreflex from mainly increases in CO to combined cardiac and peripheral vasoconstrictor responses. We conclude that the major mechanism by which the arterial baroreflex buffers the muscle metaboreflex is inhibition of metaboreflex-mediated peripheral vasoconstriction.

THE MUSCLE METABOREFLEX is activated when intramuscular metabolites accumulate because of a mismatch between blood flow and metabolism, and this accumulation stimulates group III and IV afferent neurons within the active muscle. Activation of these nerves transmits signals to the brain stem, which elicits a reflex increase in sympathetic nerve activity and systemic arterial blood pressure (10, 11, 27). The reflex acts to partially restore blood flow to the hypoperfused muscle (22). This muscle metaboreflex mediated-pressor response is attributable to increases in cardiac output (CO) and peripheral vasoconstriction (12, 18, 39).

Previous studies showed that during mild to moderate exercise the pressor response primarily depends on increased CO to improve the ischemic condition in active skeletal muscles (16, 18, 39). If a reduction in blood flow to active skeletal muscle occurs when there is sufficient cardiac reserve during mild to moderate exercise, the metaboreflex will increase CO and thus the total amount of blood flow available to active skeletal muscle. O’Leary and Augustyniak (18) demonstrated that activation of the muscle metaboreflex in conscious dogs during dynamic exercise produced significant increases in CO via the reflex tachycardia with constant stroke volume (SV), and this was the major mechanism causing the reflex increase in arterial pressure. However, when CO is at or near maximal levels, the ability of the metaboreflex to increase blood flow to ischemic active skeletal muscle may become limited and a rise in arterial pressure occurs solely via peripheral vasoconstriction (18).

The arterial baroreceptor reflex is the primary short-term regulator of systemic blood pressure via modulation of CO and peripheral vasoconstriction to maintain normal arterial pressure (24). Increased arterial pressure results in an arterial baroreflex-mediated decrease in heart rate (HR) and sympathoinhibition, whereas decreased arterial pressure results in an arterial baroreflex-mediated increase in HR and sympathoexcitation. However, both arterial pressure and HR increase simultaneously during dynamic exercise. This situation is explained by a rapid resetting of the operating point of the arterial baroreflex to a higher pressure generated during dynamic exercise (5, 17, 26, 28). Neural input from arterial baroreceptors plays an important role in regulating the cardiovascular responses during exercise. Afferent input from arterial baroreceptors and ascending input from skeletal muscle receptors synapse in the nucleus tractus solitarii of the medulla (7, 14). The arterial baroreceptor reflex modifies the pressor responses evoked by the muscle metaboreflex (25, 32). Previous investigators showed that the pressor reflexes to static muscle contraction in anesthetized animals as well as metaboreflex activation during mild exercise in conscious animals were greater after denervation of the arterial baroreceptors and concluded that arterial baroreflexes attenuate the pressor response initiated by activation of skeletal muscle afferents (32, 37). Together, these findings suggest that afferent input of the arterial baroreceptors acts as an inhibitory signal during dynamic exercise to oppose sympathoexcitation induced by activation of skeletal muscle afferents (25, 26, 32, 38). However, the extent to which the arterial baroreflex modifies the mechanisms mediating muscle metaboreflex pressor responses is unknown. Therefore, the purpose of this study was to investigate whether the rise in blood pressure initiated by the muscle metaboreflex is primarily due to the contribution of CO or peripheral vasoconstriction during mild and moderate exercise after chronic sinoaortic denervation (SAD). We hypothesized that muscle metaboreflex activation would increase sympathetic nerve activity and systemic arterial pressure and that the larger metaboreflex-mediated pressor response after barodenervation would primarily depend on enhanced peripheral vasoconstriction.
Materials and Methods

All experiments were performed with seven conscious dogs (20–25 kg) of either gender (3 male and 4 female) selected for their willingness to run on a motor-driven treadmill. Each dog was studied in the normal state and after arterial barodenervation. All procedures were reviewed and approved by the Wayne State University Animal Investigation Committee.

Surgical Preparation. All animals were surgically instrumented in the same manner, allowing the same animal to be used for multiple studies. The animals were prepared in a series of four sterile surgical sessions with at least 1 wk between surgeries and between the last surgery and the first experiment. For all procedures the animals were anesthetized with intravenous Pentothal Sodium and maintained with isoflurane. In procedures involving both left thoracotomy and retroperitoneal abdominal surgeries, the animal was treated with a transdermal fentanyl patch (Duragesic; Janssen Pharmaceutica), which delivered at a dose of 125–150 μg/h for 3 days, for analgesia. Immediately before and after each surgery Cefazolin (500 mg iv) and then Cephalexin (30 mg/kg by mouth, 2 times/day) were given to avoid postoperative infection. During recovery from surgery, buprenorphine (0.015 mg/kg iv) and acepromazine (0.1 mg/kg im) were administered for pain control and sedation whenever deemed necessary.

In the first surgical session, a left thoracotomy was performed at the fourth intercostal space and a blood flow transducer (Transonic Systems, 20 mm) was positioned around the ascending aorta to monitor CO. A second blood flow transducer (3 mm) was positioned around the left circumflex coronary artery to measure coronary blood flow. Two sonomicrometry crystals were implanted in the myocardium of the left ventricle, and three stainless steel ventricular pacing electrodes were sutured to the apex of the left ventricle for studies unrelated to the present investigation. The pericardium was reapproximated, and the chest was closed in layers.

In the second surgical session, through a left retroperitoneal abdominal approach, blood flow probes (10 and 3 mm; Transonic Systems) were placed on the left iliac artery and left renal artery to measure hindlimb (HLBF) and renal (RBF) blood flow, respectively. A pneumatic vascular occluder (In Vivo Metrics) was placed on 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 to measure mean arterial pressure (MAP) was placed in a side branch of the aorta proximal to the HLBF probe and occluder. All cables, wires, occluder tubing, and catheters were tunneled subcutaneously and exteriorized between the scapulae.

Baroreceptor Denervation. All animals underwent bilateral arterial baroreceptor denervation in two unilateral surgical procedures separated by 1–2 wk. The denervation was accomplished by transection of the aortic depressor and the carotid sinus nerves as described by Augustyniak et al. (2) and subtracted from the observed pressor response to yield MAPactive, which reflects the rise in MAP due to the metaboreflex activation. Thereafter, to calculate the percent contribution of regional vasoconstriction and CO in mediating the pressor response to the muscle metaboreflex were calculated with the following equations:

\[\Delta P_{CO} = \frac{CO_{max}}{TVC_{CR} - \Delta HVC_{CR-Max}} - P_{CR}\]

\[\Delta P_{NIVC} = \frac{CO_{Cr}/(NIVC_{Max} + HVC_{Cr})} - P_{CR}\]

where TVC is total vascular conductance (calculated as CO/MAP) and subscripts Max and CR indicate the observed responses during the maximal level of metaboreflex activation and the control value before occlusion. Thus \(\Delta P_{CO}\) shows the predicted change in MAP during hindlimb occlusion if only changes in CO occurred. \(\Delta P_{NIVC}\) shows the predicted change in MAP during hindlimb occlusion if only changes in NIVC occurred. \(P_{CR}\) is the control level of MAP before metaboreflex activation. Thereafter, to calculate the percent contribution of regional vasoconstriction and CO, the numbers obtained from Eqs. 1 and 2 are divided by MAPactive.

Statistical Analysis. Data are expressed as means ± SE. A paired t-test was used for determining differences in the hemodynamic responses to baseline data and comparing the percent contribution of CO and NIVC to muscle metaboreflex-mediated pressor response before and after arterial barodenervation during mild and moderate exercise. For hemodynamic data collected during exercise, a two-way ANOVA with repeated measures was performed for comparison with respect to arterial baroreceptor condition and metaboreflex activation. If significant interaction was found, comparison between individual means was performed by a test for simple effects post hoc analysis (Systat 8.0).
RESULTS

Table 1 shows the baseline hemodynamic parameters in the animals before and after SAD. Resting MAP was slightly but not significantly higher after SAD. HR and HLBF were significantly higher after SAD. CO, RVC, and NIVC did not differ, but SV was significantly lower after SAD. In control, on average a 4.4 μg/kg intravenous bolus of phenylephrine caused MAP to increase by 16.2 ± 1.7 mmHg and HR rapidly decreased by 36 ± 5 beats per minute (bpm). In contrast, on average after SAD only 2.4 μg/kg caused a 43.8 ± 8.4 mmHg increase in MAP and a 1 ± 5 bpm increase in HR, indicating that the SAD procedure was quite successful.

Figure 1 shows an example of the hemodynamic responses in a intact animal during free-flow mild exercise and with reduction in HLBF. The substantial reduction in hindlimb perfusion from the free-flow state elicited marked increases in CO and MAP, whereas NIVC remained relatively constant.

Hemodynamic response to metaboreflex activation during mild exercise. Figure 2 shows the hemodynamic responses in CO, HR, SV, MAP, NIVC, RVC, and HLBF to metaboreflex activation before and after SAD during mild exercise. HLBF was reduced to the same levels before and after SAD. Repeated-measures two-way ANOVA indicated a significant interactive effect (arterial baroreceptor condition × metaboreflex activation treatment) in CO, SV, and NIVC. The muscle metaboreflex substantially increased CO in both groups of animals, but the increase in CO was significantly attenuated after arterial barodenervation. There was significant reduction in SV after the arterial barodenervation compared with the intact animals during free-flow exercise and after metaboreflex activation. After arterial barodenervation, NIVC was significantly decreased during free-flow exercise and metaboreflex activation resulted in a further significant reduction compared with no change in control experiments. Although no interaction was observed, significant arterial barodenervation and metaboreflex activation effects in MAP, HR, and RVC occurred. SAD resulted in significantly higher MAP during free-flow exercise and after metaboreflex activation. MAP was significantly increased from free-flow exercise in both conditions after metaboreflex activation. At the maximal level of aortic occlusions, HR significantly increased in both conditions, but arterial barodenervation elicited higher HR during free-flow exercise and after metaboreflex activation than during control experiments. The muscle metaboreflex significantly decreased RVC in both settings, but during free flow exercise RVC was significantly lower after SAD. These results indicate that the rise in arterial pressure with metaboreflex activation in intact animals during mild exercise is due solely to the increase in CO. However, the larger increase in arterial pressure initiated by the muscle metaboreflex activation after arterial barodenervation is due mainly to a marked vasoconstriction in the nonischemic vascular beds in addition to increases in CO.

As previously observed (1), metaboreflex activation during mild exercise did not elicit any significant change in CVC (0.46 ± 0.07 vs. 0.52 ± 0.07 ml min⁻¹ mmHg⁻¹) and this response was unchanged after SAD (0.40 ± 0.04 vs. 0.39 ± 0.03 ml min⁻¹ mmHg⁻¹); furthermore, there was no significant effect of SAD on CVC.

Hemodynamic response to metaboreflex activation during moderate exercise. Figure 3 shows the hemodynamic data for CO, HR, SV, MAP, NIVC, RVC, and HLBF in response to metaboreflex activation before and after SAD during moderate exercise. HLBF was reduced to the same levels before and after SAD, confirming the successful procedure. The SAD procedure was performed on animals under anesthesia to avoid possible stress-related effects. After arterial barodenervation, HR was significantly increased in both conditions after metaboreflex activation. At the maximal level of aortic occlusions, HR significantly increased in both conditions, but arterial barodenervation elicited higher HR during free-flow exercise and after metaboreflex activation than during control experiments. The muscle metaboreflex significantly decreased RVC in both settings, but during free flow exercise RVC was significantly lower after SAD. These results indicate that the rise in arterial pressure with metaboreflex activation in intact animals during moderate exercise is due solely to the increase in CO. However, the larger increase in arterial pressure initiated by the muscle metaboreflex activation after arterial barodenervation is due mainly to a marked vasoconstriction in the nonischemic vascular beds in addition to increases in CO.
after SAD. ANOVA revealed a significant interactive effect (arterial baroreceptor condition × metaboreflex activation treatment) in CO, SV, MAP, and NIVC, and these hemodynamic responses occurred with a pattern similar to that observed during mild exercise. There was no difference in MAP during free-flow exercise after SAD. Metaboreflex activation significantly increased MAP from free-flow exercise in both settings, and, furthermore, the increase in MAP after arterial barodenervation was almost double compared with the intact animals. A metaboreflex activation effect was observed in HR and RVC in both settings. These results observed during moderate exercise also demonstrated that the greater pressor response induced by muscle metaboreflex activation occurs mainly because of a substantial vasoconstriction in the nonischemic vascular beds. Similar to the responses during mild exercise, no significant change in CVC occurred with metaboreflex activation before (0.60 ± 0.07 vs. 0.60 ± 0.06) or after SAD (0.51 ± 0.06 vs. 0.46 ± 0.03), although there was a significant SAD effect on CVC.

Table 2 indicates the absolute increases in MAP observed with the maximal levels of hindlimb occlusion in each setting during mild and moderate exercise. With hindlimb occlusion,

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Fig. 2. Averaged hemodynamic values (n = 7) at free-flow mild exercise and muscle metaboreflex activation before and after sinoaortic denervation (SAD). Filled bars, control values during free-flow exercise (C); hatched bars, muscle metaboreflex activation (MR). Asterisks between horizontal brackets reflect a significant effect of arterial baroreceptor denervation, and asterisks between vertical brackets reflect a significant effect of metaboreflex activation (P < 0.05). *Significantly different from control (P < 0.05); #significantly different from control values or values after metaboreflex activation before SAD. HR, heart rate (bpm, beats/min); SV, stroke volume; RVC, renal vascular conductance.

Fig. 3. Averaged hemodynamic values (n = 7) at free-flow moderate exercise and muscle metaboreflex activation before and after SAD. Symbols and bars same as in Fig. 2.
MAP was significantly higher after SAD during mild and moderated exercise compared with the control experiments. Relative contributions of CO and NIVC to muscle metaboreflex pressor response. Figure 4 shows the percent contributions of CO and NIVC to the pressor response during metaboreflex activation before and after SAD. In intact animals, the reflex increase in MAP was solely due to the increase in CO during mild and moderate exercise. In contrast, after arterial baroreceptor denervation, the contribution of CO to the pressor response initiated by metaboreflex activation was significantly reduced, whereas the contribution of NIVC was markedly increased. Thus these results indicate that peripheral vasoconstrictions become more important in mediating the pressor response during muscle metaboreflex activation after arterial baroreceptor denervation.

DISCUSSION

The major new finding of this study is that the arterial baroreflex has a marked impact on both the strength and mechanisms of the muscle metaboreflex. As observed previously, in normal animals the major mechanism utilized by the muscle metaboreflex to raise arterial pressure during submaximal exercise is an increase in CO, with little if any net change in peripheral vascular conductance to nonischemic areas (16, 18, 39). This increase in arterial pressure is attenuated by arterial and cardiopulmonary baroreflexes (3, 32). However, the arterial baroreflex not only modifies the strength of the muscle metaboreflex but markedly changes the mechanisms mediating the muscle metaboreflex pressor response. After SAD a significantly smaller increase in CO occurred with metaboreflex activation, yet the pressor response was significantly greater. This larger pressor response occurred because in this setting in addition to an increase in CO (albeit attenuated from control experiments), substantial decreases in peripheral vascular conductance to nonischemic areas occurred. Thus SAD shifted the mechanisms of the muscle metaboreflex from mainly increases in CO to combined cardiac and peripheral vasoconstrictor responses.

Effect of SAD on cardiovascular response at rest. Acute SAD results in substantial increases in arterial blood pressure and HR, but over time, MAP and HR return toward control levels, although it is still unknown what causes this restoration (4, 29, 36). In contrast, other groups demonstrated that, in humans, carotid sinus denervation resulted in a long-term increase in average blood pressure (33, 34). Thus there is still controversy about whether the arterial baroreceptors are involved in the long-term control of blood pressure. In the present study, we found that there was no significant difference in MAP between the intact and SAD animals, although there was a significant tachycardia after SAD, arterial pressure tended to be higher, and pressure variability was certainly greater after SAD, as has been observed previously. We only measured pressure at rest for ~5 min rather than the longer-term recording (i.e., 24 h) performed in previous studies (4, 29, 30, 36).

Effect of SAD on metaboreflex-mediated pressor response during exercise. It is generally accepted that the baroreflex is reset to a higher pressure during exercise with little change in sensitivity, and this allows the arterial pressure to increase with exercise (5, 17, 26, 28). Several investigators have shown that arterial baroreceptors act as an inhibitory signal during exercise to oppose sympathoexcitation (25, 37, 38). Sheriff et al. (32) examined the extent to which arterial baroreflexes attenuate the increase in the pressor response evoked by the muscle metaboreflex during mild exercise in conscious dogs. These investigators found that the metaboreflex-induced pressor response during dynamic exercise doubled after SAD and concluded that the arterial baroreflex opposes the pressor response initiated by the muscle metaboreflex. We also found that with SAD the pressor response (MAPactive) mediated by the muscle metaboreflex activation was almost double compared with that of the intact dogs during mild and moderate exercise (although it should be noted that the SAD procedure also removed arterial chemoreceptors, which may affect the responses). However, these previous studies only measured changes in MAP. We extend these previous studies by demonstrating that the arterial baroreflex modifies not only the strength, but also the mechanisms, of the muscle metaboreflex pressor response.

During mild exercise, we found arterial baroreceptor condition and metaboreflex activation treatment effects in both HR and MAP after SAD. Both MAP and HR during free-flow
exercise and after metaboreflex activation were significantly higher after SAD. Matsukawa et al. (9) suggested that central command contributes to the rise in sympathetic activity with spontaneous locomotion, evoking increases in both blood pressure and HR, and in turn the arterial baroreflex counteracts this increase in sympathetic activity, but with SAD this buffering is abolished.

**Arterial baroreflex vs. muscle metaboreflex: cardiac output vs. peripheral vasoconstriction.** Our laboratory demonstrated previously (1, 2, 18) that in normal dogs during mild to moderate exercise, the mechanism mediating the pressor response initiated by muscle metaboreflex activation depends primarily on an increase in CO. In contrast, we previously observed in dogs (3) that the pressor response to bilateral carotid occlusion is mediated via peripheral vasoconstriction at rest and across a broad range of workloads. Similar results to carotid unloading were subsequently observed in humans (2, 13, 23). Thus normally during submaximal exercise the muscle metaboreflex raises pressure by increases in CO and the carotid baroreflex raises pressure by increases in peripheral vasoconstriction. These observations indicate that the muscle metaboreflex has stronger control over sympathetic activity to the heart, whereas the arterial baroreflex exerts stronger control over sympathetic activity to the peripheral vasculature. The present data would support this conclusion. After SAD, marked peripheral vasoconstriction occurred with metaboreflex activation in addition to an increase in CO (although this rise in CO was attenuated from control experiments). Thus it appears that the major mechanism by which the arterial baroreflex buffers the muscle metaboreflex is inhibition of metaboreflex-mediated peripheral vasoconstriction.

The vascular bed most responsible for the peripheral vasoconstriction with metaboreflex activation after SAD is unknown. There was no significant change in the RVC responses to metaboreflex activation after SAD, although at submaximal workloads a significant portion of the RVC responses may be independent of sympathetic tone and reflect an autoregulatory response to the increase in CO. Similarly, the CVC responses were also not significantly different with metaboreflex activation after SAD. However, changes in CVC are dependent on both neurogenic α-adrenergic vasoconstrictive effects and vasodilatory stimuli due to increased ventricular function. Both before and after SAD, marked increases in myocardial oxygen demand occurred with metaboreflex activation, inasmuch as significant increases in HR and CO occurred and this increased CO was pumped against a higher afterload (MAP). Although the increase in CO was attenuated after SAD, the rise in afterload was markedly greater (see Table 2). Thus substantial vasodilatory stimuli still existed in the myocardium with metaboreflex activation after SAD. Whether the increase in cardiac sympathetic activity with metaboreflex activation was substantially greater after SAD is not known, although the similar HR responses would indicate that this is not the case. In contrast, in all likelihood sympathetic activity to the peripheral vasculature was much higher with metaboreflex activation after SAD, as evidenced by the substantial decreases in NIVC and the markedly increased contribution of this mechanism to the pressor response (Fig. 4). Circulating vasoconstrictor hormones may also be elevated with metaboreflex activation after SAD, inasmuch as we previously concluded (19) that the arterial baroreflex markedly suppresses metaboreflex-induced release of vasopressin.

Although the major target vascular bed(s) for this increased peripheral vasoconstriction with metaboreflex activation after SAD were not revealed in the present study, previous observations from our laboratory (3, 20) have shown that, as workload increases, vasoconstriction in active skeletal muscle becomes a progressively more important component of the pressor response to carotid occlusion. Indeed, as skeletal muscle blood flow becomes a progressively larger fraction of CO, the potential ability of this vascular bed to regulate arterial pressure also increases proportionally (15), and at high workloads the majority of the carotid pressor response is due to vasoconstriction in the active skeletal muscle. Thus it is likely that at least a portion of the reduction in NIVC with metaboreflex activation after SAD was due to vasoconstriction within the active skeletal muscle. If this is the case, then during submaximal workloads the arterial baroreflex normally functions to prevent the muscle metaboreflex from vasoconstricting the active skeletal muscle.

Even in barointact dogs there exist situations in which activation of the muscle metaboreflex does evoke peripheral vasoconstriction. When exercise workload is at or near maximal, induced hindlimb ischemia causes little if any further increase in CO and the major mechanism of the metaboreflex pressor response is vasoconstriction (2). Similarly, in dogs with congestive heart failure, the ability of the muscle metaboreflex to raise CO is virtually abolished and the pressor response occurs via peripheral vasoconstriction even at submaximal workloads (6). In both cases there is a likely less buffering by the arterial baroreflex. During severe exercise in normal dogs, the rise in MAP with hindlimb ischemia is attenuated (2), and in heart failure the strength of the arterial baroreflex is impaired both at rest (24) and during exercise (8). The extent to which the arterial baroreflex and muscle metaboreflex interact in heart failure is unknown.

The muscle metaboreflex cardiac response was significantly altered after SAD. The magnitude of the reflex increases in CO was depressed after SAD during both mild and moderate exercise. Although a sustained tachycardiac response was observed, a smaller increase in CO occurred because of a concomitant fall in SV compared with a small but significant increase in SV in control experiments. The mechanisms mediating this attenuation in the CO response after SAD are unknown. Metaboreflex activation resulted in a substantially greater increase in ventricular afterload after SAD, which could act to decrease SV. In addition, there may be less of an increase in ventricular performance with metaboreflex activation after SAD (21). Recent studies using rats concluded that there is an increase in cardiac apoptosis and cardiac remodeling after chronic SAD compared with sham-operated controls (31, 35). Cardiac damage induced after SAD could lessen the ability to increase ventricular contractility.

In summary, to our knowledge, this is the first study to investigate the relative contributions of CO and peripheral vasoconstriction in mediating the pressor response to muscle metaboreflex activation during mild to moderate exercise after SAD. We demonstrated that the pressor response induced by metaboreflex activation is greater after SAD during both mild and moderate exercise and that the contribution of peripheral vasoconstriction to the pressor response is markedly increased.
but that of raising CO is lessened. Thus the present study suggests that vasoconstriction in nonischemic vascular beds plays an important role in the pressor response to metaboreflex activation after SAD during dynamic exercise and that the major mechanism by which the arterial baroreflex buffers the muscle metaboreflex is limiting peripheral vasoconstriction.

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GRANTS

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