Attenuated muscle metaboreflex-induced pressor response during postexercise muscle ischemia in renovascular hypertension

Marty D. Spranger, Jasdeep Kaur, Javier A. Sala-Mercado, Tiago M. Machado, Abhinav C. Krishnan, Alberto Alvarez, and Donal S. O’Leary

Department of Physiology and Cardiovascular Research Institute, Wayne State University School of Medicine, Detroit, Michigan

Submitted 6 November 2014; accepted in final form 27 January 2015

Spranger MD, Kaur J, Sala-Mercado JA, Machado TM, Krishnan AC, Alvarez A, O’Leary DS. Attenuated muscle metaboreflex-induced pressor response during postexercise muscle ischemia in renovascular hypertension. Am J Physiol Regul Integr Comp Physiol 308: R650–R658, 2015. First published January 28, 2015; doi:10.1152/ajpregu.00464.2014.—During dynamic exercise, muscle metaboreflex activation (MMA; induced via partial hindlimb ischemia) markedly increases mean arterial pressure (MAP), and MAP is sustained when the ischemia is maintained following the cessation of exercise (postexercise muscle ischemia, PEMI). We previously reported that the sustained pressor response during PEMI in normal individuals is driven by a sustained increase in cardiac output (CO) with no peripheral vasoconstriction. However, we have recently shown that the rise in CO with MMA is significantly blunted in hypertension (HTN). The mechanisms sustaining the pressor response during PEMI in HTN are unknown. In six chronically instrumented canines, hemodynamic responses were observed during rest, mild exercise (3.2 km/h), MMA, and PEMI in the same animals before and after the induction of HTN [Goldblatt two kidney, one clip (2K1C)]. In controls, MAP, CO and HR increased with MMA (+52 ± 6 mmHg, +2.1 ± 0.3 l/min, and +37 ± 7 beats per minute). After induction of HTN, MAP at rest increased from 97 ± 3 to 130 ± 4 mmHg, and the metaboreflex responses were markedly attenuated (+32 ± 5 mmHg, +0.6 ± 0.2 l/min, and +11 ± 3 bpm). During PEMI in HTN, HR and CO were not sustained, and MAP fell to normal recovery levels. We conclude that the attenuated metaboreflex-induced HR, CO, and MAP responses are not sustained during PEMI in HTN.

exercise pressor reflex; postexercise circulatory occlusion; peripheral resistance; hypertension

THE MUSCLE METABOREFLEX is a very powerful blood pressure-raising reflex (1, 3, 12, 22, 42, 48, 51, 65). Metabolically sensitive afferents of this reflex (group III/IV) are stimulated by metabolites (e.g., protons, lactate, potassium, and diprotinated phosphate), which accumulate within underperfused active skeletal muscle (10, 19, 30, 32, 35, 46, 47, 56–58, 61). Muscle metaboreflex activation results in a reflex increase in sympathetic outflow (9, 28–30, 36–38, 62). During submaximal dynamic exercise, metaboreflex activation markedly increases heart rate (HR), cardiac output (CO) and left ventricular dp/dt max, with little effect on the peripheral vasculature (5, 16, 17, 26, 27, 55, 60, 65). Therefore, the substantial metaboreflex-mediated pressor response observed during mild dynamic exercise is virtually solely the result of the increase in CO.

In contrast, when metaboreflex activation is maintained following the cessation of submaximal dynamic exercise (postexercise muscle ischemia, PEMI) in normal subjects, the pressor response is sustained despite a decrease in HR toward resting levels with a time course similar to normal recovery from exercise (1, 2, 21, 44, 49, 50, 62–64). The fall in HR during PEMI led some investigators to question the role of CO in mediating the sustained pressor response during PEMI (21, 49, 50, 63). We recently demonstrated that the sustained pressor response during PEMI following metaboreflex activation during submaximal dynamic exercise is principally driven by elevated CO, not peripheral vasoconstriction (60). The sustained elevation in CO during PEMI is driven by enhanced chronotropy coupled with a sustained or slightly elevated stroke volume (SV), which is supported by enhanced inotropy (dp/dt max) and lusitropy (dp/dt min), a pattern seen with metaboreflex activation during exercise (13, 16, 17, 27, 42, 52, 60). Therefore, the mechanisms mediating muscle metaboreflex-induced increases in mean arterial pressure (MAP) are similar regardless of whether the reflex is activated during dynamic exercise or if it is sustained during the recovery from dynamic exercise (60).

We recently reported attenuated metaboreflex-induced chronotropic, inotropic, and lusitropic responses during submaximal dynamic exercise after induction of hypertension (HTN) (51). Several studies from our group (4, 5, 26, 27, 43, 54) and others (15) have demonstrated a “switch” from a flow-mediated to a vasoconstriction-mediated pressor response during exercise when the reflex increase in CO is artificially attenuated (27, 54) or when there is a physiological inability to increase CO, such as during severe exercise (5) or in heart failure (4, 15, 26, 43). Thus, it appears that whether or not increases in CO or peripheral vasoconstriction is utilized as a means to raise MAP with metaboreflex activation during dynamic exercise is dependent on the ability to increase CO.

The mechanisms sustaining the pressor response during PEMI in HTN are unknown. Inasmuch as metaboreflex-induced increases in HR, CO, and dp/dt max are markedly attenuated in HTN, we tested the hypothesis that the sustained pressor response during PEMI would be principally supported by increased peripheral vasoconstriction.

METHODS

Experimental Subjects

Six adult female mongrel canines were selected for the study. All animals were healthy, ~20–25 kg body wt, well adapted to the laboratory environment, and willing to run on a motor-driven treadmill. We did not intentionally select females; rather the sex of the animals was based on the availability of animals from our vendor. We...
have previously shown that sex has no effect on the strength or mechanisms of the muscle metaboreflex (33). No experiments were performed when the animal was in estrus. During experimentation, all animals exercised voluntarily, and no negative reinforcement techniques were utilized. The protocols developed and employed in the present study were reviewed and approved by the Institutional Animal Care and Use Committee of Wayne State University and complied with the National Institutes of Health’s Guide to the Care and Use of Laboratory Animals.

Surgical Procedures

The animals were prepared, as described previously (51). Briefly, in the first sterile surgical procedure (left thoracotomy), an ultrasonic perivascular flow probe was positioned around the ascending aorta to measure CO. A flow probe was also placed around the left circumflex artery to measure coronary blood flow for studies unrelated to the present investigation. Lastly, the catheter of an implantable telemetry blood pressure transmitter was inserted into the left ventricle to measure left ventricular pressure (LVP). In the second surgical procedure, ultrasonic perivascular flow probes were placed around the terminal aorta and left renal artery for measuring hindlimb blood flow (HLBF) and renal blood flow (RBF), respectively. Two perivascular hydraulic occluders were positioned around the terminal aorta (distal to the flow probe) to provide the means to incrementally reduce HLBF to engage the muscle metaboreflex. One perivascular hydraulic occluder was positioned around the left renal artery (distal to the flow probe) to reduce RBF to induce HTN [two kidney, one clip (2K1C) Goldblatt model]. Lastly, a catheter was secured into the terminal aorta (cranial to the flow probe and occluders) to measure arterial pressure.

Following both surgical procedures, buprenorphine (0.05 mg/kg iv) and acepromazine (0.5 mg/kg im) were administered for analgesia and sedation, respectively. The animals were treated with cefazolin (30 mg/kg iv) preoperatively and postoperatively and with cephalexin (30

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>96.9 ± 2.9</td>
<td>129.5 ± 3.7*</td>
</tr>
<tr>
<td><strong>CO, l/min</strong></td>
<td>3.45 ± 0.20</td>
<td>3.56 ± 0.26</td>
</tr>
<tr>
<td><strong>TPR, mmHg·l⁻¹·min</strong></td>
<td>28.7 ± 2.2</td>
<td>37.4 ± 3.1*</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>101.8 ± 3.6</td>
<td>124.8 ± 4.4*</td>
</tr>
<tr>
<td><strong>CO, l/min</strong></td>
<td>4.91 ± 0.32</td>
<td>4.92 ± 0.25</td>
</tr>
<tr>
<td><strong>TPR, mmHg·l⁻¹·min</strong></td>
<td>21.4 ± 2.0</td>
<td>25.8 ± 1.8*</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>153.5 ± 4.9</td>
<td>156.7 ± 6.5</td>
</tr>
<tr>
<td><strong>CO, l/min</strong></td>
<td>7.03 ± 0.60</td>
<td>5.49 ± 0.36*</td>
</tr>
<tr>
<td><strong>TPR, mmHg·l⁻¹·min</strong></td>
<td>22.6 ± 2.0</td>
<td>29.0 ± 1.8*</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>151.5 ± 5.0</td>
<td>142.6 ± 6.8</td>
</tr>
<tr>
<td><strong>CO, l/min</strong></td>
<td>5.19 ± 0.49</td>
<td>4.08 ± 0.38*</td>
</tr>
<tr>
<td><strong>TPR, mmHg·l⁻¹·min</strong></td>
<td>28.5 ± 2.1</td>
<td>36.0 ± 2.6*</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. MAP, mean arterial pressure; CO, cardiac output; TPR, total peripheral resistance; REST, rest; EX, exercise; MMA, muscle metaboreflex activation; PEMI, postexercise muscle ischemia. *P < 0.05 normal vs. hypertension.

Fig. 1. Time course of mean arterial pressure (MAP), vascular conductance, cardiac output (CO), heart rate (HR), stroke volume (SV), and hindlimb blood flow (HLBF) during rest, mild exercise, muscle metaboreflex activation (MMA), and PEMI before (normal) (dashed black lines) and after induction of hypertension (solid black lines) in one animal. Data represented are the final 60 s of steady-state data during rest, exercise and MMA. 60 s of PEMI immediately followed the MMA steady state.
mg/kg po, twice daily) prophylactically for the term of the experimental protocol. The animals were allowed a minimum of 10 days for recovery between surgical procedures and before running control experiments.

Data Acquisition

After complete postoperative recovery, each animal was brought into the laboratory and allowed to roam freely and acclimate for ~15–20 min. The animal was then directed onto the treadmill where the instrumentation was connected to the data acquisition system. CO, HLBF, and RBF flow probe cables were connected to transit-time perivascular flow meters (TS420; Transonic Systems). The LVP telemetry signal was collected by a receiver connected to a calibrated analog adapter and a barometric pressure reference device (RMC-1, R11CPA, APR-1, respectively; Data Sciences International). The arterial catheter was connected to a pressure transducer (Transpac IV, ICU Medical). All hemodynamic variables, in addition to MAP (calculated) and HR (triggered by the CO signal), were monitored as beat-by-beat averages and real-time waveforms by a data acquisition system (LabScribe, iWorx) and recorded for subsequent off-line analysis.

Induction of Hypertension

After completion of control experiments, HTN was induced via a Goldblatt 2K1C model (23, 24). Blood flow to the left kidney was reduced to a target level of ~30% of baseline via partial inflation of the renal vascular occluder. HTN gradually developed over the next several weeks. We defined HTN as systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg. The experiments were repeated after 31.5 ± 3.4 days of sustained HTN.

Experimental Design

Each animal performed two experimental protocols before (normal) and after induction of HTN, and, therefore, each animal served as its own control. On each day, the experimental protocol sequence was randomized to avoid any order effect. All experiments began with the animal standing unrestrained on the treadmill until all hemodynamic resting data were observed to be stable (~5–10 min). The treadmill was turned on, and the speed was gradually increased to 3.2 km/h at 0% grade (mild exercise for a canine). Steady-state exercise was generally reached within 3–5 min and then one of the following protocols was performed.

Free-Flow Exercise and Postexercise Recovery

Following steady-state exercise, the treadmill was abruptly stopped, and hemodynamic data were collected for 60 s, while the animal was standing still during postexercise recovery (without ischemia; that is, free-flow).

Muscle Metaboreflex Activation and Postexercise Muscle Ischemia

Following steady-state exercise, the metaboreflex was engaged during exercise via partial reductions in HLBF, and steady-state data were collected for 60 s. The treadmill was then abruptly stopped and the occlusion was sustained for an additional 60 s while the animal was standing still.

Data Analysis

CO, HLBF, LVP, HR, and MAP data were continuously recorded during each experiment. Other hemodynamic parameters were calculated off-line [e.g., SV, nonischemic vascular conductance (NIVC), total peripheral resistance (TPR), and dP/dt_max and dP/dt_min]. Because of technical difficulties, we were only able to obtain dP/dt_max and dP/dt_min data for five animals. One-minute averages of steady-state data were calculated at rest, during exercise, and during metaboreflex activation. Five-second averages were computed for the 60 s of postexercise recovery and PEMI. Responses for these two settings were taken as the average of the last 10 s. Differences between these responses were calculated to compare the effect of PEMI vs. postexercise recovery before and after induction of hypertension.

Statistical Analysis

Averaged responses for each animal were analyzed via two-way repeated-measures ANOVA to compare hemodynamic data for time and/or condition effects. In the event of a significant time-condition interaction, a C-matrix test for simple effects was performed. Data are reported as means ± SE, and statistical significance was ascribed as P < 0.05.
RESULTS

MAP was significantly elevated at rest following the induction of HTN, which was due to an increase in TPR (Table 1). TPR values during MMA and PEMI reflect changes in vascular tone and the mechanical effects of the vascular occluder; therefore, we used NIVC to quantify vascular responses (60).

Figure 1 shows responses in MAP, NIVC, CO, HR, SV, and HLBF from one animal, and Fig. 2 shows the mean values during rest, mild dynamic exercise, muscle metaboreflex activation, and PEMI before (normal) and after induction of HTN.

The 60 s of PEMI in Fig. 2 are plotted as 5-s averages. Following induction of HTN, MAP was significantly higher, HR and CO were unchanged, and NIVC was significantly lower at rest and during mild exercise. HLBF was not different during mild exercise prior to metaboreflex activation before and after induction of HTN (1.2 ± 0.1 l/min in both settings). HLBF was reduced to similar levels to induce muscle metaboreflex activation (0.5 ± 0.04 l/min control and 0.4 ± 0.04 l/min in HTN) and was similarly maintained during PEMI. Metaboreflex-induced increases in MAP, HR, CO, and NIVC were markedly attenuated following induction of HTN. HR, CO, and NIVC were significantly lower than normal during the entire 60 s of PEMI following induction of HTN, while MAP was not significantly different.

Figure 3 shows mean values of MAP, NIVC, CO, HR, SV, dP/dt_{max} and dP/dt_{min} during rest, mild exercise, and the final averaged 10 s of postexercise recovery before and after induction of HTN. Resting MAP and dP/dt_{max} were significantly elevated. NIVC was significantly reduced, and CO, HR, SV, and dP/dt_{min} were similar to normal following induction of HTN. NIVC, CO, HR, and dP/dt_{max} significantly increased from rest to mild exercise, while MAP, SV and dP/dt_{min} were unchanged. Following induction of HTN, NIVC was reduced during exercise, CO and HR significantly increased as in normal, while MAP, SV, and dP/dt_{max} and dP/dt_{min} were similar to rest. During the final averaged 10 s of postexercise recovery, MAP, SV, and dP/dt_{min} remained unchanged, while NIVC, CO, HR, and dP/dt_{max} fell to levels not significantly different from those observed at rest (P > 0.05). Following induction of HTN, NIVC was significantly reduced and dP/dt_{max} significantly elevated with respect to normal, and both parameters fell to rest (P > 0.05; rest vs. postexercise recovery).

Figure 4 shows mean values of MAP, NIVC, CO, HR, SV, dP/dt_{max} and dP/dt_{min} during rest, mild exercise, muscle metaboreflex activation, and the final 10 s of PEMI before and after induction of HTN. All hemodynamic responses at rest and during mild exercise before and after induction of HTN were similar as shown in Fig. 3. All cardiovascular parameters significantly increased with muscle metaboreflex activation; however, following induction of HTN, metaboreflex-induced increases were markedly attenuated. During the final 10 s of PEMI, all parameters fell significantly below metaboreflex activation levels and, with the exception of NIVC, all remained significantly elevated above postexercise recovery levels (see Fig. 5). Following induction of HTN, SV, dP/dt_{max} and dP/dt_{min} remained at metaboreflex activation levels, while MAP, NIVC, CO, and HR fell to levels not significantly different from postexercise recovery (see Fig. 5).

![Fig. 3. Mean hemodynamic responses in MAP, NIVC, CO, HR, SV, dP/dt_{max} and dP/dt_{min} during rest, mild exercise (EX), and the final 10 s of postexercise recovery (POST-EX) before (open bars) and after induction of HTN (solid bars). *P < 0.05 between normal and HTN. †P < 0.05 from previous setting.](http://ajpregu.physiology.org/doi/abs/10.1152/ajpregu.00464.2014)
Figure 5 shows mean steady-state changes in MAP, NIVC, CO, HR, SV, dP/dmax and dP/dmin between the final averaged 10 s of postexercise recovery (see Fig. 3) and the final averaged 10 s of PEMI (see Fig. 4) before and after induction of HTN. The changes in MAP, CO, HR SV, dP/dmax, and dP/dmin between PEMI and postexercise recovery were significantly smaller following the induction of HTN, while changes in NIVC were not significantly different.

DISCUSSION

Our major new finding is that the attenuated muscle metaboreflex-induced pressor response in HTN is not sustained during PEMI. The attenuated rise in CO with metaboreflex activation in HTN falls back toward resting levels with a time course similar to normal recovery from mild exercise and with no apparent exaggerated peripheral vasoconstriction; arterial pressure is only slightly above resting levels, which likely reflects the passive, hydraulic effects of the imposed hindlimb occlusion. Thus, the markedly reduced ability to raise CO with metaboreflex activation in HTN during dynamic exercise also extends to during PEMI, which, thereby, limits any reflex pressor response.

Muscle metaboreflex activation during exercise in normal subjects elicits a substantial pressor response, which is sustained during PEMI (1, 6, 8, 16–18, 21, 22, 39, 44, 48, 55, 61, 64). We recently demonstrated that this sustained pressor response during PEMI is supported by a sustained increase in CO and not peripheral vasoconstriction (60). The sustained CO during PEMI was driven by enhanced chronotropy coupled with a sustained SV, which was supported by enhanced inotropy and lusitropy. Thus, the mechanisms mediating metaboreflex-induced pressor responses are similar both when the reflex is activated during dynamic exercise and when the reflex is sustained during the recovery from exercise (PEMI) (8, 16–18, 44, 48, 60). Several studies have demonstrated a “switch” from a flow-mediated to a vasoconstriction-mediated pressor response during exercise when the ability of the reflex to increase CO is experimentally or pathologically restrained (5, 15, 26, 27, 54). In the present study, we observed substantially attenuated metaboreflex-induced CO and MAP responses in HTN as recently shown by Sala-Mercado et al. (51). We observed only a hint toward increased metaboreflex-induced vasoconstriction after induction of HTN. In most previous studies using this or similar preparations (including the present study) metaboreflex activation causes a small increase in vascular conductance in the nonischemic beds. In preliminary studies, we found that this could be blocked by a β-adrenergic antagonist, indicating potential epinephrine release during metaboreflex activation. After induction of HTN, this small vasodilation was abolished. Whether this is due to reduced β-receptor-mediated vasodilation or enhanced sympathetic α-adrenergic receptor-mediated vasoconstriction (or both) is unknown. After induction of HTN, the pressor response during PEMI was not sustained via either sustained increases in CO or enhanced peripheral vaso-
constriction. During PEMI, CO, HR, dP/dt_{max}, and dP/dt_{min} fell to normal recovery levels and, despite a downward baseline shift in NIVC during all settings, the recovery pattern of NIVC was similar to control, indicating no increase in peripheral vasoconstriction. Therefore, the attenuated pressor response was not sustained during PEMI in HTN. Because both CO and NIVC fell to levels not significantly different from those during normal recovery, the small level of pressor response likely stemmed from the hydraulic effects of the occluder per se.

Few studies have investigated muscle metaboreflex function during PEMI in HTN, and the findings are equivocal. Farquhar and colleagues (20, 25) recently demonstrated in elderly hypertensive humans that the pressor response to static handgrip exercise (30 – 40% MVC) is exaggerated in HTN and sustained during PEMI. Similar findings have been reported in prehypertensive humans performing static handgrip exercise (11, 31). However, in a previous study from Farquhar and colleagues (53), the pressor response to rhythmic handgrip exercise (60% MVC) was not exaggerated in HTN, yet MAP was sustained during PEMI. Similar findings have been reported in prehypertensive humans performing static handgrip exercise (11, 31). However, in a previous study from Farquhar and colleagues (53), the pressor response to rhythmic handgrip exercise (60% MVC) was not exaggerated in HTN, yet MAP was sustained during PEMI. In contrast, Rondon et al. (45) did not find an exaggerated pressor response to static handgrip exercise (30% MVC) in humans with untreated HTN, and blood pressure fell to baseline during PEMI. While the lack of a sustained pressor response during PEMI in the hypertensive groups is in agreement with the present study, the absence of a sustained pressor response during PEMI in the normotensive group is perplexing. The lack of congruency of the present and aforementioned studies may be due to several factors, including differences in species, age, type, and intensity of exercise performed, experimental methodology, and the underlying etiology of the hypertension. We discussed several of these issues in a previous study (60).

Studies by Farquhar and colleagues (20, 25) have reported sustained elevations in muscle sympathetic nerve activity during PEMI in HTN, indicating possible enhanced peripheral vasoconstriction. However, as CO was not measured in these studies, to what extent CO contributed to the maintenance of MAP during PEMI is unknown. The conflicting results of the present study and those from Farquhar and colleagues is potentially due to differences in exercise intensity and the muscle group, in which the reflex was evoked. For example, CO responses are often seen during PEMI following more intense exercise with a large muscle group, whereas with PEMI following lower-intensity exercise with smaller muscle groups, the pressor response usually occurs primarily via peripheral vasoconstriction (8, 16, 18, 55). In our model, we robustly activated the metaboreflex by inducing hindlimb ischemia in an exercise workload, wherein hindlimb blood flow constitutes about 10% of cardiac output, whereas Farquhar and colleagues (20, 25) elicited the reflex from one arm after 30 – 40% MVC static contractions. In general, with PEMI following leg exercise, HR and CO remain elevated, while with PEMI following moderate arm exercise, there is little HR or CO response (2, 21, 44). Therefore, it is possible that the experimental model of Farquhar and colleagues is one that is driven by peripheral vasoconstriction and not CO. Indeed, previous studies both

Fig. 5. Mean steady state changes in MAP, NIVC, CO, HR, SV, dP/dt_{max}, and dP/dt_{min} between the final averaged 10 s of postexercise recovery and the final averaged 10 s of PEMI before (open bars) and after induction of HTN (solid bars). *P < 0.05 between normal and HTN.
support (8, 16–18, 44, 48, 55, 60) and refute (6, 18, 44) any role for CO in mediating the pressor response during PEMI. As such, we would not expect the pressor response to fall during PEMI in HTN as in our model.

Several factors could potentially contribute to impaired metaboreflex-induced increases in cardiac function during sub-maximal dynamic exercise in HTN, as previously discussed (51). One previous study concluded that metaboreceptors are sensitized in HTN; therefore, impaired receptor function likely is not a cause of the attenuated responses we observed (41). Others have demonstrated impaired cardiac responses stemming from reduced β-adrenergic receptor function (7, 66) and density (40). Inasmuch as the mechanisms mediating muscle metaboreflex-induced increases in arterial pressure are similar both during and immediately following (PEMI) submaximal dynamic exercise, these factors could contribute to the impaired maintenance of chronotropy, inotropy, and CO observed during PEMI in the present study. We previously demonstrated in normal subjects that metaboreflex-induced increases in sympatheic nerve activity vasoconstrict the coronary vasculature, thereby limiting the rise in coronary blood flow and impairing ventricular function (13) and that this coronary vasoconstriction is exaggerated in heart failure, which further exacerbates the ventricular dysfunction (14). To what extent metaboreflex activation during exercise in HTN leads to coronary vasoconstriction and impaired ventricular performance is unknown. It is also possible that the blunted metaboreflex-induced pressor response waned more quickly with washout of the metabolites during recovery since we employed incomplete occlusion in our model to engage the muscle metaboreflex, and/or complete vasculature isolation may not have occurred.

**Perspectives and Significance**

We (60) and others (8, 16–18, 44, 48, 55) have demonstrated in normal subjects that CO sustains the pressor response during PEMI. In contrast, other investigators have concluded that elevated arterial pressure stems from peripheral vasoconstriction, not CO (6, 18, 44). Several factors could account for these disparate conclusions, including differences in species, age, type, and intensity of exercise performed and experimental methodology. Recently, we reported that metaboreflex-induced increases in arterial pressure are markedly attenuated in HTN when the reflex is activated during dynamic exercise (51). In contrast, several investigators have concluded that the metaboreflex is exaggerated in prehypertension and HTN in both humans (11, 20, 25, 31) and spontaneously hypertensive rats (34, 41, 59). In the present study, metaboreflex-induced CO and HR responses were markedly attenuated, and the mechanisms sustaining the pressor response during PEMI were altered as CO and HR fell to normal recovery levels. Moreover, the recovery pattern of NIVC during PEMI was similar to control, indicating no increase in peripheral vasoconstriction. Therefore, the attenuated pressor response was not sustained during PEMI in HTN. While these findings in renovascular HTN are consistent with some previous findings in human essential HTN (45), they are inconsistent with other studies (20, 25). To what extent the etiology of HTN affects these responses is not known.

**ACKNOWLEDGMENTS**

The authors thank Jody Helme-Day for expert animal care and technical assistance.

**GRANTS**

This study was supported by National Heart, Lung, and Blood Institute Grants HL-55743 and HL-095819. This study was also funded by the Multidisciplinary Research Group Incubator Program at Wayne State University.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


