Attenuated arterial baroreflex buffering of muscle metaboreflex in heart failure

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Submitted 17 June 2005; accepted in final form 25 July 2005

Kim, Jong-Kyung, Javier A. Sala-Mercado, Robert L. Hammond, Jaime Rodriguez, Tadeusz J. Scislo, and Donal S. O’Leary. Attenuated arterial baroreflex buffering of muscle metaboreflex in heart failure. Am J Physiol Heart Circ Physiol 289: H2416–H2423, 2005. First published July 29, 2005; doi:10.1152/ajpheart.00654.2005.—Previous studies have shown that heart failure (HF) or sinoaortic denervation (SAD) alters the strength and mechanisms of the muscle metaboreflex during dynamic exercise. However, it is still unknown to what extent SAD may modify the muscle metaboreflex in HF. Therefore, we quantified the contribution of cardiac output (CO) and peripheral vasoconstriction to metaboreflex-mediated increases in mean arterial blood pressure (MAP) in conscious, chronically instrumented dogs before and after induction of HF in both barointact and SAD conditions during mild and moderate exercise. The muscle metaboreflex was activated via partial reductions in hindlimb blood flow. After SAD, the metaboreflex pressor responses were significantly higher with respect to the barointact condition despite lower CO responses. The pressor response was significantly lower in HF after SAD but still higher than that of HF in the barointact condition. During control experiments in the barointact condition, total vascular conductance summed from all beds except the hindlimbs did not change with muscle metaboreflex activation, whereas in the SAD condition both before and after induction of HF significant vasoconstriction occurred. We conclude that SAD substantially increased the contribution of peripheral vasoconstriction to metaboreflex-induced increases in MAP, whereas in HF SAD did not markedly alter the patterns of the reflex responses, likely reflecting that in HF the ability of the arterial baroreflex to buffer metaboreflex responses is impaired.

sinoaortic denervation; exercise; cardiac output; arterial baroreflex; exercise pressor response

DURING DYNAMIC EXERCISE, group III and IV afferent neurons within the active skeletal muscle are stimulated when metabolites accumulate because of a decrease in the ratio of oxygen supply to oxygen demand. These sensory neurons relay information to the central nervous system and elicit a powerful pressor response termed the muscle metaboreflex (8, 12, 21, 27). Activation of the muscle metaboreflex during mild to moderate exercise elicits increases in heart rate (HR), cardiac output (CO), mean arterial blood pressure (MAP), ventricular performance, central blood volume mobilization, and vasoconstriction in the renal and nonischemic skeletal muscle vasculature (6, 13, 18–21, 28, 34). The major mechanism mediating the rise in MAP during submaximal dynamic exercise in normal dogs is the large increase in CO, which thereby partially restores blood flow and O2 delivery to the ischemic active skeletal muscle (6, 18, 20, 25, 28, 34). The large pressor response arising from stimulation of skeletal muscle afferents is opposed by the arterial baroreflex (11, 29, 33). Our laboratory recently demonstrated (11) that the restraint of the muscle metaboreflex pressor response by the arterial baroreflex occurs mainly via baroreflex inhibition of metaboreflex-induced peripheral vasoconstriction.

It is well known that chronic heart failure (HF) is characterized by abnormalities in the regulation of autonomic function. A recent study from our laboratory investigated the effects of HF on the strength and mechanisms of the muscle metaboreflex in conscious dogs. Hammond et al. (6) found that activation of the muscle metaboreflex during mild and moderate exercise still evoked a significant pressor response after induction of HF, but the mechanisms of this pressor response were changed compared with those observed in control experiments. The normal large reflex increase in CO was virtually abolished, and thus the pressor response occurred via peripheral vasoconstriction. Others have also observed altered responses to stimulation of skeletal muscle afferents in HF. Smith et al. (32) observed a larger pressor response to static muscle contractions in decerebrate rats in HF. In addition, Silber et al. (30) observed accentuated activation of the muscle metaboreflex during rhythmic static contractions in human subjects with HF, and Notarius et al. (16) also observed greater sympathoactivation during ischemic or intense nonischemic arm exercise in HF. Accentuated activation of the reflex during exercise may stem from underperfusion of the active skeletal muscle (7, 30).

The mechanisms involved in this change in metaboreflex response patterns with HF remain unresolved. Previous investigators demonstrated that arterial baroreceptor gain is decreased in dogs with HF (4, 14). Inasmuch as the arterial baroreflex buffers the muscle metaboreflex mainly by limiting peripheral vasoconstriction (11), with the reduced arterial baroreflex strength in HF, presumably less buffering of metaboreflex-induced peripheral vasoconstriction could potentially occur. Therefore, the purpose of the present study was to determine whether the extent of buffering of the muscle metaboreflex by the arterial baroreflex is attenuated in HF. We hypothesized that the effect of arterial baroreceptor denervation on the mechanisms of the muscle metaboreflex pressor response would be less in animals with HF vs. that observed in normal subjects.

METHODS

All experiments were performed with conscious dogs of either sex selected for willingness to run on a motor-driven treadmill. Two
Baroreceptor denervation was confirmed by lack of change in HR in response to a rapid rise in MAP induced by intravenous bolus infusion of phenylephrine. In control experiments, a 4.3 μg/kg intravenous bolus of phenylephrine increased MAP by 15.2 ± 1.6 mmHg and HR rapidly decreased by 32 ± 3 beats/min. In contrast, after SAD, an intravenous bolus of only 2.3 μg/kg of phenylephrine resulted in a 40.1 ± 7.5 mmHg increase in MAP and no significant change in HR occurred (+4 ± 5 beats/min). No animal was excluded from the study because of incomplete SAD. In this final surgical procedure, a catheter was also inserted into the jugular vein and advanced to the atrial-caval junction to measure CVP.

**Experimental procedures.** All experiments were performed after at least 1 wk of recovery. Experiments were performed in the same animals before and after induction of HF in both barointact and SAD conditions; thus as much as possible each animal served as its own control (see Table 1). Each animal was taken to the laboratory and allowed to roam freely for 15–30 min. The animals were led to the treadmill, and the blood flow transducers were connected to the flowmeters (Transonic Systems). The MAP and CVP catheters were connected to pressure transducers (Transpac IV; Abbott Laboratories). All flow and pressure transducers were coupled to a Gould recording system (model RS 3800). HR was monitored via a cardiotachometer triggered by the CO signal. A laboratory computer sampled all data, and mean values for each cardiac cycle were saved on hard disk for subsequent data analysis.

Data at rest were recorded with the animals standing quietly on the treadmill. The treadmill was started at either mild (3.2 km/h, 0% grade) or moderate (6.4 km/h, 10% grade) work intensities, and after 3–5 min all data reached steady state. The muscle metaboreflex was activated during exercise by partial occlusion of the terminal aorta. The degree of occlusion of hindlimb perfusion was increased until substantial increases in MAP occurred. We attempted to reduce HLBF to the same levels in each condition within each animal; however, during mild exercise after induction of HF, hindlimb perfusion was reduced to slightly lower levels (<10% difference from other conditions, see results).

**Postbaroreceptor denervation.** The animals were studied from 1 to 3 wk after baroreceptor denervation. The experimental protocol was conducted as described above. HF was induced by rapid left ventricular pacing at 225–250 beats/min for ~30 days, utilizing a fixed-rate pacemaker built in our laboratory. Threshold values for pacing voltage and pulse width that were necessary for ventricular capture were determined by means of a pacing system analyzer (model 5311b; Medtronic).

**Data analysis.** One-minute averages of all variables were taken during steady state at rest, during exercise, and during hindlimb vascular occlusion. The average values of MAP, HR, CO, coronary vascular conductance [\(CVC = RBF/(MAP - CVP)\)], RBF, renal vascular conductance [\(RVC = RBF/(MAP - CVP)\)], and nonischemic vascular conductance [\(NIVC = (CO - HLBF)/(MAP - CVP)\)] were collected before and in response to hindlimb vascular occlusion. NIVC reflects the sum of all regional vascular conductances except the hindlimbs. In animals 7–13 CVP was not measured during control barointact experiments, and therefore conductance values were calculated only with MAP. This reflects only a small error inasmuch as CVP is low and does not change with metaboreflex activation in normal animals (28). With partial vascular occlusion of the terminal aorta, MAP can rise via the mechanical effects of partial aortic occlusion, e.g., decreasing vascular conductance to the hindlimbs by inflating the occluder will increase arterial pressure independently of any reflexes due to the mechanical reduction in total vascular conductance. This increase in MAP by the passive mechanical effects of the occluder was calculated as described by Augustyniak et al. (2) and subtracted from the observed pressor response to yield MAP\text{active}, which reflects the rise in MAP due to the reflex (e.g., via increases in CO and/or peripheral vasoconstriction). All muscle metaboreflex increases in MAP described here reflect MAP\text{active}.

### Table 1. Distribution of experimental states

<table>
<thead>
<tr>
<th>Barointact</th>
<th>HF</th>
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Animals studied in each setting are shown. No. of animals observed in each setting: barointact control (n = 13); barointact heart failure (HF) (n = 6); sinoaortic baroreceptor denervation (SAD) control (n = 7); SAD HF (n = 5).
Statistical analysis. Data are expressed as means ± SE. For hemodynamic data collected at rest and during exercise, multiple linear regression analysis was performed to assess the contribution of different treatment effects (arterial baroreceptor condition and HF) on the responses to exercise and muscle metaboreflex activation as described by Slinker and Glantz (31). This is analogous to a two-way ANOVA for repeated measures but allows the use of all data across all conditions for all paired observations (see Table 1). An interaction term was also included in the regression. If the interaction term was statistically significant, comparisons between individual means were performed with modified Bonferroni tests. Statistical significance was accepted if $P < 0.05$.

RESULTS

Table 2 shows the baseline hemodynamic data collected at standing rest before and after induction of HF in barointact and SAD dogs. Resting CO, stroke volume (SV), MAP, and HLBF were significantly lower after induction of HF, whereas HR and CVP were significantly increased compared with the pre-HF state. Resting MAP and HR were significantly higher after SAD, whereas SV was significantly decreased compared with the barointact condition. There was no significant difference in NIVC in HLBF after SAD.

Hemodynamic responses to dynamic exercise. Figure 1 shows the hemodynamic values during free-flow mild exercise before metaboreflex activation before and after induction of HF in barointact and SAD dogs. There was a significant effect of HF on CO, SV, and HLBF, and furthermore, SV decreased significantly after SAD with respect to the barointact condition. MAP was significantly higher in SAD vs. the barointact condition, but after induction of HF MAP was significantly decreased compared with the control values in both barointact and SAD conditions. HR increased significantly with HF before and after SAD. CVP significantly increased after HF in both barointact and SAD conditions. NIVC was not significantly different before and after HF in both barointact and SAD condition but tended to be attenuated after SAD.

Figure 2 shows the hemodynamic responses during free-flow moderate exercise before metaboreflex activation before and after HF in barointact and SAD dogs. Similar results occurred in CO, MAP, CVP, and HLBF as observed during mild exercise. HR significantly increased after HF in the SAD condition and was slightly but not significantly higher after HF in the barointact condition. SV was depressed after HF compared with control in both intact and SAD conditions and tended to be attenuated after SAD. There was no significant difference in NIVC between control and HF before and after SAD.

Hemodynamic responses to metaboreflex activation during mild exercise. Figure 3 shows the absolute changes in hemodynamic values in response to metaboreflex activation during mild exercise before and after induction of HF in barointact and SAD dogs. Metaboreflex activation resulted in significant increases in CO before HF in both barointact and SAD conditions, but after induction of HF little if any reflex increase occurred in CO both before and after SAD. SAD also significantly decreased the CO response compared with the barointact condition. In barointact normal animals, SV increased with muscle metaboreflex activation, whereas after HF SV decreased and after SAD SV decreased in both control experiments and after induction of HF. On activation of the metaboreflex, MAP was significantly higher in SAD compared with the values before and after HF in barointact condition. With metaboreflex activation, the rise in MAP was significantly lower in HF after SAD and tended to be attenuated after HF in barointact condition. With metaboreflex activation, NIVC significantly decreased in HF compared with the control values in both conditions and significantly decreased after SAD with respect to the barointact condition. These results indicate that with metaboreflex activation a greater pressor response after SAD was due to substantial peripheral vasconstriction as well as an increase in CO. There was no difference in the reflex tachycardia before and after HF in both barointact and SAD conditions. With metaboreflex activation, CVC significantly decreased after HF as previously observed, and after SAD the CVC response was significantly reduced. Although we attempted to decrease HLBF to the same levels in each condition, HLBF was slightly lower with occlusion (<10%) after induction of HF, which resulted in a statistically significant HF effect ($0.63 ± 0.07$, $0.58 ± 0.1$, $0.58 ± 0.05$, $0.53 ± 0.02$ l/min for normal barointact, HF barointact, SAD, SAD + HF, respectively).

Hemodynamic responses to metaboreflex activation during moderate exercise. Figure 4 shows the absolute changes in the hemodynamic data in response to metaboreflex activation during moderate exercise before and after HF and before and after SAD. Similar results occurred in the CO and SV responses as observed during mild exercise. Metaboreflex activation significantly increased MAP before and after HF in SAD compared with the barointact condition, whereas the pressor response was significantly depressed after induction of HF. After HF, elicitation of the metaboreflex resulted in a significant reduction of NIVC in the barointact condition. The reflex also significantly decreased NIVC after SAD, and furthermore, NIVC tended to decrease after HF in the SAD condition. With metaboreflex activation CVC also decreased significantly after HF in the barointact condition, but this variable did not change after SAD. After SAD the metaboreflex resulted in significantly larger increase in HR. There was no statistically significant difference in the lowest imposed

Table 2. Baseline hemodynamic data

<table>
<thead>
<tr>
<th>Condition</th>
<th>CO, l/min</th>
<th>HR, beats/min</th>
<th>SV, ml</th>
<th>MAP, mmHg</th>
<th>NIVC, ml/min l/mmHg</th>
<th>CVP, mmHg</th>
<th>HLBF, l/min</th>
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<tr>
<td>Intact</td>
<td>4.82 ± 0.27</td>
<td>105 ± 4</td>
<td>46.2 ± 2.7</td>
<td>104.4 ± 2.4</td>
<td>39.55 ± 2.30</td>
<td>5.92 ± 0.94</td>
<td>0.82 ± 0.07</td>
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<tr>
<td>Intact-HF</td>
<td>4.03 ± 0.27 †</td>
<td>123 ± 7*</td>
<td>33.5 ± 3.2*</td>
<td>85.3 ± 2.5*</td>
<td>43.64 ± 2.64</td>
<td>10.42 ± 0.79*</td>
<td>0.75 ± 0.01*</td>
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<tr>
<td>SAD</td>
<td>4.69 ± 0.20</td>
<td>124 ± 4†</td>
<td>38.2 ± 2.2†</td>
<td>118.2 ± 4.9†</td>
<td>34.53 ± 2.98</td>
<td>4.32 ± 0.42</td>
<td>0.83 ± 0.07</td>
</tr>
<tr>
<td>SAD-HF</td>
<td>3.35 ± 0.31 †</td>
<td>137 ± 4‡</td>
<td>24.6 ± 2.8‡</td>
<td>94.6 ± 3.6‡</td>
<td>32.94 ± 3.88</td>
<td>10.72 ± 0.64*</td>
<td>0.61 ± 0.05*</td>
</tr>
</tbody>
</table>

Mean ± SE baseline hemodynamic data collected at standing rest for barointact and SAD dogs. CO, cardiac output; HR, heart rate; SV, stroke volume; MAP, mean arterial blood pressure; NIVC, nonischemic vascular conductance; CVP, central venous pressure; HLBF, hindlimb blood flow. *Significant HF effect ($P < 0.05$); †significant arterial baroreceptor denervation effect ($P < 0.05$).
levels of HLBF during muscle metaboreflex activation across all conditions (1.94 ± 0.99, 1.87 ± 0.23, 1.70 ± 0.15, 1.57 ± 0.90 l/min for normal barointact, HF barointact, SAD, SAD + HF, respectively).

Figures 5 and 6 show the relative roles of increases in CO vs. decreases in NIVC in mediating the muscle metaboreflex-induced increases in MAP before and after HF and before and after SAD during mild (Fig. 5) and moderate (Fig. 6) exercise.

At both workloads, in the normal animal virtually all of the reflex increase in MAP was due to the substantial rise in CO. As observed previously, this pattern is shifted toward combined increases in CO with substantial peripheral vasoconstriction after SAD (11). In contrast, after induction of HF the mechanism of the muscle metaboreflex completely shifts to peripheral vasoconstriction with little change in CO. After SAD in animals with HF, the pattern of the muscle metaboreflex responses is little changed compared with the HF animals before SAD, e.g., the reflex increase in MAP still occurs via peripheral vasoconstriction.
DISCUSSION

The major new finding in this study is that after induction of HF in animals with SAD, activation of the muscle metaboreflex still elicits a significant pressor response but it is substantially smaller than that observed in normal animals before or after SAD and the mechanisms mediating the pressor response reflect a pattern similar to that observed in HF before SAD. In HF, the mechanisms of the pressor response mediated by this reflex are markedly altered compared with those observed in control animals both before and after SAD. In the normal animal during submaximal exercise the primary mechanism utilized by the muscle metaboreflex is to increase CO. After both HF and SAD, substantial peripheral vasoconstriction now occurs with metaboreflex activation (6, 11). However, in HF the CO component of the reflex is virtually abolished and all of the pressor response occurs via peripheral vasoconstriction (6), whereas after SAD the pressor response occurs via combined effects of increased CO and increased peripheral vasoconstriction (11). With the induction of HF in animals after SAD, the patterns of the metaboreflex mechanisms were not markedly altered, e.g., the pressor response was somewhat larger but it was still due to increased peripheral vasoconstriction with little ability to increase CO. Thus whereas SAD markedly alters the mechanisms of the muscle metaboreflex in normal animals, the effect of SAD is much less in subjects with HF. These data

Fig. 3. Absolute changes (Δ) in hemodynamic values in response to metaboreflex activation during mild exercise (3.2 km/h) before and after induction of HF in barointact and SAD conditions. Symbols as in Figs. 1 and 2. *Significantly different from barointact (normal) control; #significantly different from barointact (normal) HF.

Fig. 4. Absolute changes in hemodynamic values in response to metaboreflex activation during moderate exercise (6.4 km/h, 10% grade) before and after induction of HF in barointact and SAD conditions. Symbols as in Figs. 1–3.
indicate that the extent of arterial baroreflex buffering of the muscle metaboreflex is diminished in HF. This reduced baroreflex buffering is likely due to the depressed baroreflex strength in subjects with HF seen both at rest (4, 14) and during exercise (10).

Metaboreflex-mediated pressor response with HF after SAD. In normal animals, the pressor response mediated by the muscle metaboreflex is mainly due to an increase in CO, and this partially relieves the ischemic condition in the active skeletal muscles by increasing the total amount of blood flow available (Figs. 3 and 4; Refs. 19, 20, 25, 34). Previously, our laboratory demonstrated (1, 6, 23) that after induction of HF, CO was depressed during free-flow exercise and much smaller, if any, increases in CO occurred with metaboreflex activation due to a concomitant fall in SV despite the tachycardiac response (Figs. 3 and 4). We found similar results in this study during mild and moderate exercise. However, these previous studies only investigated the mechanisms of the metaboreflex-induced pressor response after HF in the barointact condition. For the first time, the present study observed that in HF after SAD the CO response to the metaboreflex was significantly depressed with a pattern similar to that observed after HF in barointact condition during mild and moderate exercise and that peripheral vasoconstriction plays the pivotal role in mediating the pressor response, without a significant contribution by the CO component (Figs. 5 and 6). The mechanism mediating this attenuation in the CO response after HF in SAD condition is still unknown. HF likely impairs the ability of the muscle metaboreflex to increase ventricular contractility (23), and a significant rise in blood pressure by the metaboreflex after HF in the SAD condition increases ventricular afterload (Figs. 3 and 4), which may contribute to the decrease in SV.

Despite the inability to increase CO, activation of the metaboreflex after HF in the SAD condition significantly increased MAP during mild and moderate exercise and the pressor response was significantly higher than that of HF in the barointact condition. It is likely that the greater increase in MAP after HF in the SAD condition compared with that of HF in barointact condition is due to the fact that the muscle metaboreflex is not buffered by the arterial baroreflex after SAD, whereas in HF before SAD the arterial baroreflex still inhibits the metaboreflex-mediated pressor response (albeit the sensitivity of the arterial baroreflex is reduced after HF in the barointact condition). Another likely explanation is that after SAD vasopressin increases with muscle metaboreflex activation (15), because it was observed previously that the arterial baroreflex suppresses vasopressin release induced by the metaboreflex (21). A previous study also demonstrated that the metaboreflex significantly increased the release of vasopressin in HF during mild and moderate exercise (6). Together, after HF in the SAD condition, the substantial sympathetic activation as well as the release of potent vasoactive hormones by the

Fig. 5. Relative roles of increases in CO (filled bars) vs. peripheral vasoconstriction (hatched bars) in mediating the muscle metaboreflex-induced increase in MAP during mild exercise (3.2 km/h) in barointact and after SAD before and after induction of HF. *Significantly different from barointact.

Fig. 6. Relative roles of increases in CO (filled bars) vs. peripheral vasoconstriction (hatched bars) in mediating the muscle metaboreflex-induced increase in MAP during moderate exercise (6.4 km/h, 10% grade) in barointact and after SAD before (normal) and after induction of HF. *Significantly different from barointact.
metaboreflex may be the major mechanism to increase blood pressure by peripheral vasoconstriction. No humoral factors were measured in this study, and thus we do not know how much hormones contributed to the pressor response mediated by strong metaboreflex activation.

Arterial baroreflex vs. muscle metaboreflex. These two powerful reflexes are capable of substantially raising arterial pressure during exercise but normally do so via very different mechanisms. In both dogs and humans, unloading of carotid baroreceptors induces a pressor response virtually solely via peripheral vasoconstriction (3, 26). In contrast, a pressor response of similar magnitude in normal dogs via the muscle metaboreflex during submaximal exercise occurs via increases in CO with little, if any, peripheral vasoconstriction (2, 34). These data suggest that the arterial baroreflex exerts greater control over sympathetic activity to the periphery and that the muscle metaboreflex exerts greater control over sympathetic activity to the heart (although it should be noted that the arterial baroreflex can also control HR via changes in parasympathetic tone, which may lessen as workload increases and tonic parasympathetic activity decreases; Refs. 9, 22, 24). Thus arterial baroreflex buffering of the muscle metaboreflex likely occurs via baroreflex inhibition of metaboreflex-induced peripheral vasoconstriction. Our findings after SAD support this concept (11). The major mechanism mediating the much larger metaboreflex response observed after SAD in normal animals was increased peripheral vasoconstriction (11, 29). Indeed, the rise in CO was smaller with metaboreflex activation after SAD, which may reflect the markedly elevated afterload observed in this setting inasmuch as SV actually decreased significantly (Figs. 3 and 4). In HF, the ability of the muscle metaboreflex to improve ventricular function is virtually abolished (6, 23) and the pressor response occurs via peripheral vasoconstriction. Our data support the concept that this shift in the effert mechanisms of the muscle metaboreflex in HF may be due in part to a lesser ability of the arterial baroreflex to buffer metaboreflex-induced peripheral vasoconstriction.

The major vascular bed responsible for the peripheral vasoconstriction with metaboreflex activation after induction of HF before or after SAD is unknown. In all settings there was a significant reduction in RVC with metaboreflex activation, and during moderate exercise statistical analysis revealed a significant effect of both HF and SAD (data not shown). However, the reductions in RVC contribute only a small amount toward the pressor response because such a small fraction of CO is directed to the kidney (3, 17). Furthermore, the reflex fall in CVC was smaller after induction of HF in the SAD condition compared with the HF state before SAD. Thus we propose that active skeletal muscle may become a primary target for this metaboreflex-induced peripheral vasoconstriction as it does with baroreceptor unloading in both normal animals and after induction of HF (3, 10). In conscious dogs at rest, ~50% of the CO is directed to skeletal muscle (5); therefore, 50% of total vascular conductance is that to the skeletal muscle. At rest, 87% of HLBF is flow to the skeletal muscle (5). Thus in the normal animal at rest ~40% of NIVC is skeletal muscle (calculations can be made from the data shown in Table 2). During exercise, the fraction of CO directed to skeletal muscle increases considerably. Even if we assume that there was no redistribution of flow away from inactive vascular beds during exercise, the large metaboreflex-induced decreases in NIVC observed in HF or after SAD (Figs. 3 and 4) could only occur either via pronounced vasoconstriction in the active skeletal or via nearly complete vasoconstriction of all inactive beds [e.g., kidney (which did not occur), intestines, brain]. If this is indeed the case, then muscle metaboreflex-induced vasoconstriction within the active skeletal muscle in HF may exacerbate an already precarious situation.

In summary, the arterial baroreflex restrains the muscle metaboreflex primarily via inhibition of metaboreflex-induced peripheral vasoconstriction. The ability of the muscle metaboreflex to vasoconstrict the peripheral vasculature is revealed by both SAD and HF. With SAD the arterial baroreflex is inoperative, and in HF the strength of the baroreflex is reduced. Thus, in both settings, the ability of the arterial baroreflex to buffer the metaboreflex is either eliminated or reduced. The effect of SAD after induction of HF on the muscle metaboreflex is not marked, likely reflecting the impaired baroreflex function seen in HF subjects. Thus it is likely that the mechanism by which the muscle metaboreflex shifts from primarily a flow-raising reflex (increases in CO) in normal subjects to a peripheral vasoconstriction reflex in HF is that the ability to raise CO is lessened because of the ventricular dysfunction and that the ability of the arterial baroreflex to buffer metaboreflex-induced vasoconstriction is also impaired. The marked peripheral vasoconstriction seen with metaboreflex activation in SAD and HF likely reflects vasoconstriction within active skeletal muscle, but this has yet to be directly tested.

ACKNOWLEDGMENTS

We thank Sue Harris for expert technical assistance.

GRANTS

This study was supported by National Heart, Lung, and Blood Institute Grants HL-55473 and HL-67814.

REFERENCES


