

Carotid baroreflex pressor responses at rest and during exercise: cardiac output vs. regional vasoconstriction

HEIDI L. COLLINS, ROBERT A. AUGUSTYNIAK,
ERIC J. ANSORGE, AND DONAL S. O'LEARY

Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan 48201

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Collins, Heidi L., Robert A. Augustyniak, Eric J. Ansonge, and Donal S. O'Leary. Carotid baroreflex pressor responses at rest and during exercise: cardiac output vs. regional vasoconstriction. *Am J Physiol Heart Circ Physiol* 280: H642–H648, 2001.—The arterial baroreflex mediates changes in arterial pressure via reflex changes in cardiac output (CO) and regional vascular conductance, and the relative roles may change between rest and exercise and across workloads. Therefore, we quantified the contribution of CO and regional vascular conductances to carotid baroreflex-mediated increases in mean arterial pressure (MAP) at rest and during mild to heavy treadmill exercise (3.2 kph; 6.4 kph, 10% grade; and 8 kph, 15% grade). Dogs ($n = 8$) were chronically instrumented to measure changes in MAP, CO, hindlimb vascular conductance, and renal vascular conductance in response to bilateral carotid occlusion (BCO). At rest and at each workload, BCO caused similar increases in MAP (average 35 ± 2 mmHg). In response to BCO, neither at rest nor at any workload were there significant increases in CO; therefore, the pressor response occurred via peripheral vasoconstriction. At rest, $10.7 \pm 1.4\%$ of the rise in MAP was due to vasoconstriction in the hindlimb, whereas $4.0 \pm 0.7\%$ was due to renal vasoconstriction. Linear regression analysis revealed that, with increasing workloads, relative contributions of the hindlimb increased and those of the kidney decreased. At the highest workload, the decrease in hindlimb vascular conductance contributed $24.3 \pm 3.4\%$ to the pressor response, whereas the renal contribution decreased to only $1.6 \pm 0.3\%$. We conclude that the pressor response during BCO was mediated solely by peripheral vasoconstriction. As workload increases, a progressively larger fraction of the pressor response is mediated via vasoconstriction in active skeletal muscle and the contribution of vasoconstriction in inactive beds (e.g., renal) becomes progressively smaller.

carotid sinus hypotension; dog; regional vascular conductance

THE ARTERIAL BAROREFLEX FUNCTIONS as the primary short-term, negative-feedback controller of arterial pressure via modulation of cardiac output (CO) and peripheral vascular conductance to maintain arterial pressure at normal levels. However, during dynamic exercise, arterial pressure and heart rate (HR) increase. The generally accepted conclusion is that dy-

amic exercise is associated with a rapid resetting of the arterial baroreflex to a higher pressure without a change in gain (4, 13, 18–20, 22, 23). That is, the prevailing arterial pressure remains on the high-gain portion of the baroreflex function curve, and the strength of control of arterial pressure is unaltered.

Several investigators have proposed that the active skeletal muscle must be an important site for the baroreflex-mediated vasoconstriction during exercise (2, 12, 17, 22, 23, 26). This was suggested because as exercise intensity increases, active muscle vascular conductance becomes a progressively greater fraction of total vascular conductance. To test this hypothesis, O'Leary et al. (17) measured the decreases in hindlimb vascular conductance (HVC) at rest and during exercise in response to bilateral carotid artery occlusion (BCO) in conscious dogs. The magnitude of the carotid baroreflex-mediated reduction in HVC increased with exercise intensity, thus indicating that active skeletal muscle participates importantly in BCO-mediated pressor responses. However, only arterial pressure, hindlimb blood flow (HBF), and HVC were measured in that study, and thus the authors were unable to directly address the mechanism(s) contributing to the BCO-mediated pressor response. This is an important consideration, since carotid baroreflex-mediated increases in arterial pressure may be affected by changes in CO as well as peripheral vasoconstriction, and their relative roles may change with exercise intensity.

Therefore, we designed the present study to quantify the contribution of CO and peripheral vasoconstriction in mediating the pressor response to carotid sinus hypotension. We hypothesize that changes in CO will have little effect on the BCO-mediated pressor response, since it has been previously reported that carotid sinus hypotension resulted in little change in HR during rest or exercise (17, 28). Furthermore, with increasing exercise intensity, as the contribution of active skeletal muscle to total vascular conductance (TVC) increases, reflex decreases in conductance in this bed will make a greater contribution to the BCO-mediated pressor response. Conversely, with increasing exercise intensity, as the contribution of nonactive

Address for reprint requests and other correspondence: D. S. O'Leary, Dept. of Physiology, Wayne State University School of Medicine, 540 East Canfield Ave., Detroit, MI 48201 (E-mail: doleary@med.wayne.edu).

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beds (e.g., renal) to TVC decreases, vasoconstriction in these beds will contribute less to the BCO-mediated pressor response.

METHODS

All experiments were performed using eight 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 and Use Committee and conformed to the American Physiological Society's "Guiding Principles in the Care and Use of Animals."

Surgical preparation. Each animal ($n = 8$) was instrumented for chronic hemodynamic measurements in a series of three sterile surgical procedures as described in detail previously (1, 14, 15, 24). Briefly, through a left thoracotomy, a 20-mm Transonic flow probe was positioned around the ascending aorta for measurements of CO. For experimental protocols unrelated to the present study, three stainless steel ventricular pacing electrodes were sutured to the apex of the left ventricle, and in four animals a 4-mm Transonic flow probe was positioned around the circumflex artery and sonomicrometer crystals were sutured into the wall of the left ventricle. The pericardium was reapproximated, and the chest was closed in layers.

In the second surgical procedure, the abdominal cavity was exposed by means of a midline laparotomy. Transonic flow probes were placed on the terminal aorta and the left renal artery to monitor HBF and renal blood flow (RBF), respectively. A pneumatic 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 Tygon catheter was placed in a side branch of the aorta proximal to the flow probe and occluder to monitor mean arterial pressure (MAP).

In the third and final procedure, a Tygon catheter was inserted into the right jugular vein and advanced to the atrial-caval junction to monitor central venous pressure (CVP). In addition, a pneumatic vascular occluder was placed around each common carotid artery. All flow probe cables, ventricular pacing leads, occluder tubing, and catheters were tunneled subcutaneously and exteriorized between the scapulae.

Experimental design. All experiments were performed after the animals had fully recovered from the last surgery (≥ 1 wk) and were active, afebrile, and of good appetite. The responses of MAP, HR, CO, HBF, and RBF to a 2-min BCO were recorded at rest and during three levels of graded treadmill exercise ranging from mild (3.2 kph, 0% grade), to moderate (6.4 kph, 10% grade), to heavy (8 kph, 15% grade) intensities.

Data collection. The blood flow transducers were connected to the flowmeters (Transonic Systems), and MAP and CVP catheters were connected to pressure transducers (Transpac IV, Abbott Laboratories). HR was monitored via a cardiota-chometer triggered by the CO signal. All data were recorded continuously on a Gould 3800 recorder and on a laboratory computer at 1,000 Hz. Mean values for each cardiac cycle were saved on hard disk for subsequent analysis.

Experimental procedures. On the day of the experiment, the animal was brought to the laboratory and allowed to roam freely for 15–30 min. Subsequently, the dog was directed to the treadmill, and the flow probe cables and catheters were connected. With the dog standing quietly on the treadmill, baseline resting hemodynamic parameters were obtained. Subsequently, both carotid arterial occluders were

rapidly inflated for 2 min and then rapidly deflated. A 10-min recovery period was allowed before the onset of exercise. After 3–5 min of steady-state exercise, both occluders were again rapidly inflated for 2 min, the occluders were deflated, and the treadmill was shut off. The animal was allowed to recover for ≥ 30 min before a second experimental run was performed. The order of the exercise intensities was randomized. There were never more than two experiments performed on the same day.

Data analysis. Control levels of each variable were taken as the 1-min average immediately before BCO. The responses to BCO were taken as the average of the values during the last 30 s of the occlusion. At least two experiments in each setting were performed on each animal, and the responses to BCO were averaged within each animal to yield mean values for that animal at rest and at each exercise intensity. These mean values were then averaged across animals to yield mean responses for the experimental group. Thus each animal served as its own control. Because of technical difficulties, we were unable to obtain RBF data in one animal and all hemodynamic data at the highest workload in one animal.

The average values of MAP, HR, CO, HBF, HVC [i.e., HBF/(MAP – CVP)], RBF, renal vascular conductance [RVC = RBF/(MAP – CVP)], and TVC [i.e., CO/(MAP – CVP)] were obtained before (control) and in response to BCO. RBF and RVC values were doubled to account for hemodynamic responses in both kidneys. Since TVC is the sum of all regional vascular conductances, the percent contributions of regional vasoconstrictions and CO in mediating the pressor response to BCO can be directly calculated. This was achieved by calculating the predicted change in MAP during BCO if only the individual changes in CO, HVC, or RVC occurred and all other parameters remained at control levels, which thereby reflects the cardiac or regional peripheral vasoconstriction components of the pressor response. These equations are as follows

$$\text{predicted change MAP}_{\text{CO}} = [(\text{CO}_{\text{obs}}/\text{TVC}_{\text{avg control}}) + \text{CVP}_{\text{avg control}}] - \text{MAP}_{\text{avg control}} \quad (1)$$

where MAP_{CO} is the MAP response to BCO due to CO alone, CO_{obs} is the CO observed during the BCO, and $\text{TVC}_{\text{avg control}}$ and $\text{MAP}_{\text{avg control}}$ are the baseline control values averaged over 1 min before the onset of the BCO. $\text{CVP}_{\text{avg control}}$ values at rest and during mild, moderate, and heavy exercise were 3.7 ± 0.4 , 4.1 ± 0.7 , 7.5 ± 1.2 , and 9.3 ± 1.1 mmHg, respectively, and no significant changes occurred with BCO at rest or any workload. The predicted change of MAP_{HVC} is as follows

$$\text{predicted change MAP}_{\text{HVC}} = [(\text{CO}_{\text{avg control}}/\text{HVC}_{\text{obs}}) + \text{RVC}_{\text{avg control}} + \text{EVC}_{\text{avg control}} + \text{CVP}_{\text{avg control}}] - \text{MAP}_{\text{avg control}} \quad (2)$$

where $\text{EVC} = \text{TVC} - (\text{HVC} + \text{RVC})$ and represents vascular conductance elsewhere in the body. The predicted change of MAP_{RVC} is as follows

$$\text{predicted change MAP}_{\text{RVC}} = [(\text{CO}_{\text{avg control}}/\text{HVC}_{\text{avg control}}) + \text{RVC}_{\text{obs}} + \text{EVC}_{\text{avg control}} + \text{CVP}_{\text{avg control}}] - \text{MAP}_{\text{avg control}} \quad (3)$$

Equations 1–3 are similar to those recently reported from our laboratory (1). The predicted changes in MAP due to the individual responses in CO, HVC, and RVC were used to calculate the percent contribution of these individual responses to the observed reflex increase in MAP during BCO.

Table 1. Contributions of HVC, RVC, and CO to the pressor response during BCO at rest and during mild, moderate, and heavy exercise

	Rest	Exercise		
		Mild (3.2 kph)	Moderate (6.4 kph, 10% grade)	Heavy (8 kph, 15% grade)
HVC	10.68 ± 1.42	13.26 ± 2.39	20.43 ± 3.31	24.29 ± 3.38
RVC	3.98 ± 0.74	2.88 ± 0.63	1.93 ± 0.44	1.55 ± 0.27
CO	6.01 ± 7.14	12.65 ± 7.04	6.60 ± 8.13	-4.50 ± 6.53

Values are means ± SE expressed as percentages. HVC and RVC, hindlimb and renal vascular conductance, respectively; CO, cardiac output; BCO, bilateral carotid occlusion.

The averaged percent contributions of HVC, RVC, and CO to the pressor response during bilateral carotid occlusion at rest and during mild, moderate, and heavy exercise are presented in Table 1.

Statistical analysis. Values are means ± SE. A two-way ANOVA with repeated measures was used for determining differences in the hemodynamic responses to BCO at rest and

during exercise (9). Significant interactions observed by the ANOVA were further evaluated by a test for simple effects (Systat 8.0). A linear regression analysis was used to determine the relationship between the percent contribution of HVC, RVC, and CO to the carotid baroreflex-induced pressor response and as workload and baseline HBF increased (16, 17). A one-way ANOVA with repeated measures was used to determine a workload effect on the change of MAP, HVC, RVC, and CO in response to BCO. Because of the unequal variance across workloads of HVC, a logarithmic transformation of the HVC values was performed before the one- and two-way ANOVAs. An α -level of $P < 0.05$ was used to determine statistical significance.

RESULTS

Figure 1 presents an example of the hemodynamic responses to BCO in one dog at rest and during heavy exercise. BCO at rest increased MAP with little or no change in CO. Modest decreases in TVC, HVC, and RVC occurred, suggesting that peripheral vasoconstriction mediated the pressor response to BCO. Heavy exercise substantially increased MAP, CO, TVC, and

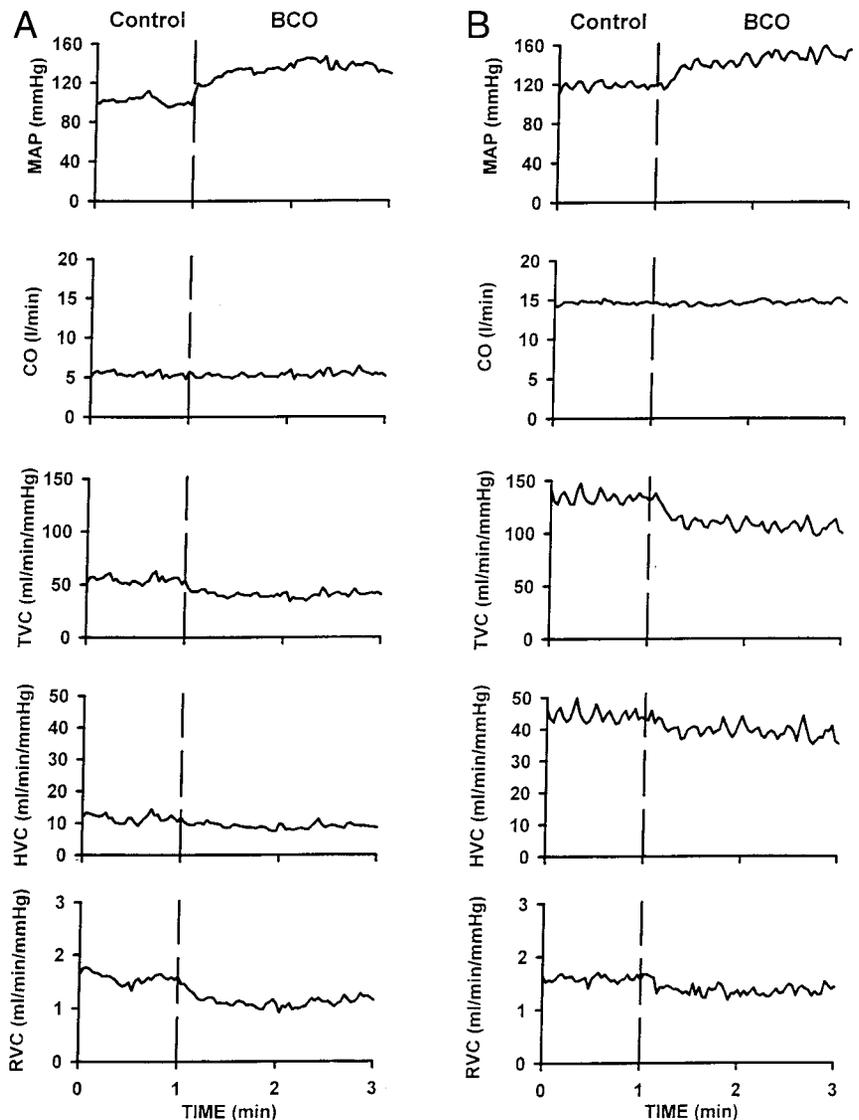


Fig. 1. Actual data from 1 animal presenting mean arterial pressure (MAP), cardiac output (CO), total vascular conductance (TVC), hindlimb vascular conductance (HVC), (A) and renal vascular conductance (RVC) at rest and during heavy exercise (8 kph, 15% grade) (B) 1 min before and during bilateral carotid occlusion (2 min). Vertical line, onset of bilateral carotid occlusion (BCO).

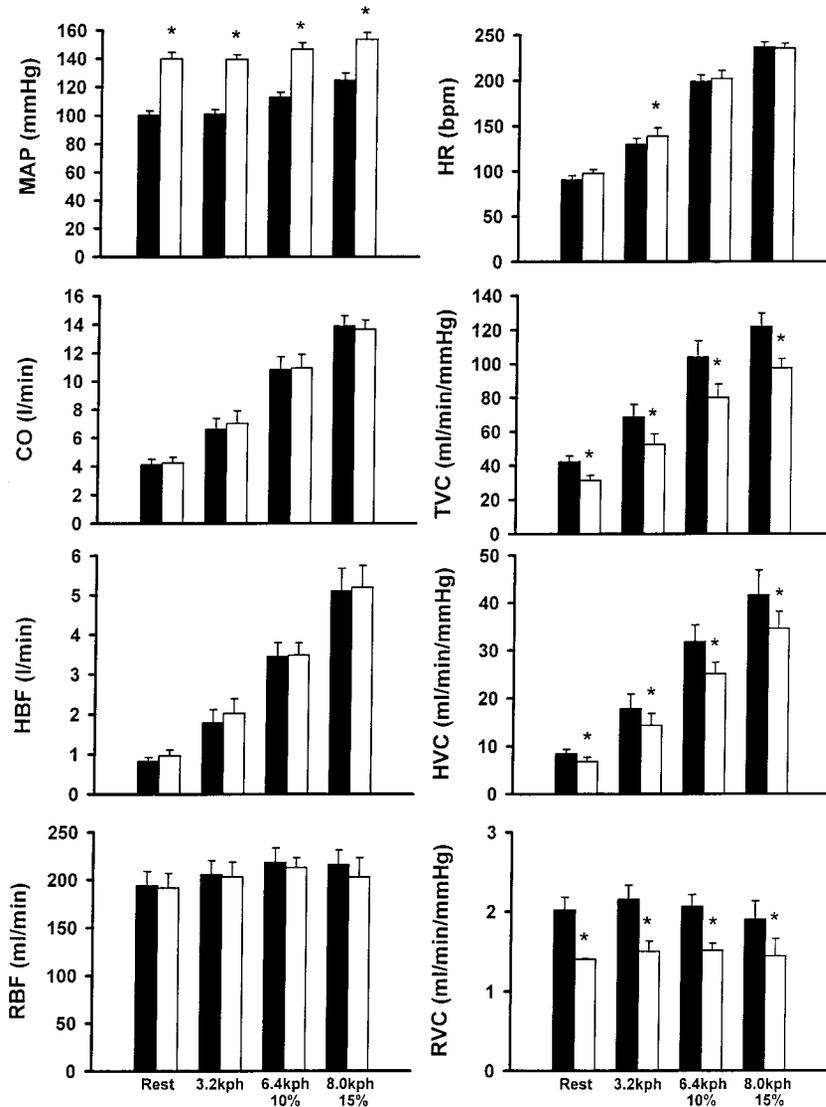


Fig. 2. Averaged hemodynamic values during control (solid bars) and in response to BCO (open bars) at rest and during 3 levels of exercise. RBF, renal blood flow; HBF, hindlimb blood flow. * $P < 0.05$, control vs. BCO.

HVC. BCO during heavy exercise induced hemodynamic responses similar to those observed at rest; however, greater decreases in TVC and HVC and a somewhat smaller decrease in RVC occurred in this animal.

Figure 2 presents the average hemodynamic responses at rest and during exercise before (control) and during BCO. A one-way ANOVA revealed similar changes in MAP during BCO at rest and across exercise intensities (average 35 ± 2 mmHg, $P = 0.071$). The reductions in TVC, RVC, and HVC in response to carotid sinus hypotension compared with control values were significant at rest and across workloads, whereas no significant change in CO occurred. Furthermore, a significant workload effect on the decrease in HVC was observed, indicating that as workload increased, a greater vasoconstrictor response in the hindlimb vascular bed occurred ($P = 0.001$). In contrast, a workload effect on the decrease in RVC was not observed. A small but statistically significant increase

in HR occurred at 3.2 kph during BCO (11 ± 5 beats/min, $P = 0.04$).

Figure 3 presents the relationship between the percent contributions of HVC, RVC, and CO to the BCO-mediated pressor response as a function of baseline HBF. Baseline HBF was used, since these values are closely related to exercise intensity (5, 11). Linear regression analysis revealed a positive correlation between the percent contribution of HVC to the pressor response and baseline HBF ($r = 0.714$), and the slope was significantly different from zero ($P < 0.001$). These results indicate that reductions in HVC contribute progressively more to the carotid baroreflex-induced pressor response with increasing workloads. Conversely, a negative correlation existed between the percent contribution of RVC to the pressor response and baseline HBF ($r = 0.700$), and the slope was also significantly different from zero ($P < 0.001$). These results indicate that reductions in RVC contribute progressively less to the carotid baroreflex-induced pres-

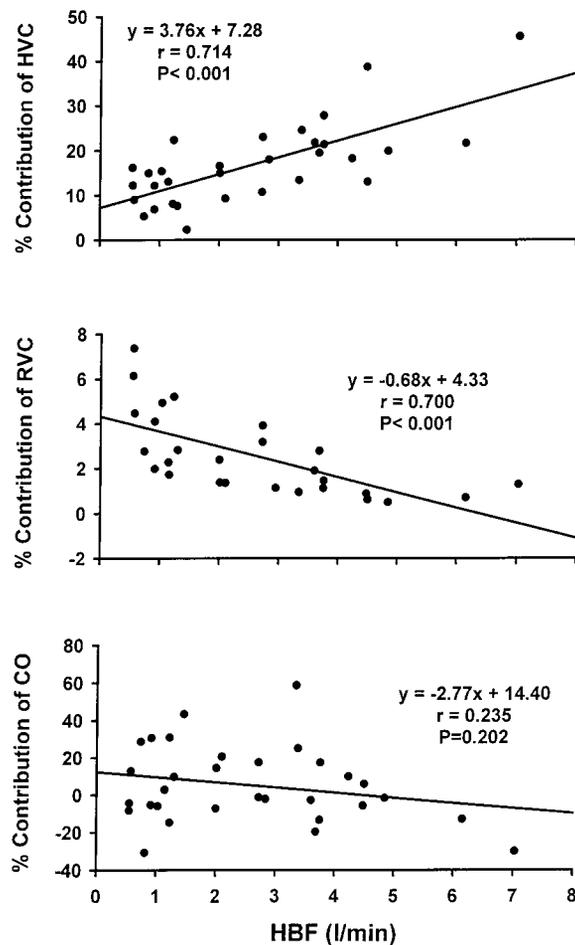


Fig. 3. Relationship among percent contributions of HVC, RVC, and CO to the pressor response during BCO and baseline HBF at rest and during exercise in all animals. Results indicate an increase in the relative contribution of the hindlimb and a decrease in the contribution of the kidney to the carotid baroreflex-induced pressor response with increasing workloads. $P < 0.05$; slope was significantly different from zero.

sor response with increasing workloads. Finally, a significant relationship between the percent contribution of CO and baseline HBF was not observed ($r = 0.235$, $P > 0.05$).

DISCUSSION

The major finding in this study is that neither at rest nor at any workload were there significant increases in CO during BCO, indicating that the pressor response to carotid sinus hypotension is mediated solely by peripheral vasoconstriction. Furthermore, active skeletal muscle becomes an increasingly more important target vasculature for carotid baroreflex-induced vasoconstriction as exercise intensity rises. This was demonstrated by progressively larger contributions of reductions in HVC to the pressor response during carotid sinus hypotension as exercise intensity increased (Fig. 3). Furthermore, as exercise intensity increases, the renal vascular bed becomes a progressively less impor-

tant site for carotid baroreflex-induced vasoconstriction (Fig. 3).

The magnitude of the reduction in TVC during carotid sinus hypotension increased as workload increased. The contribution of a given change in regional vascular conductance to the regulation of blood pressure is dependent on the level of TVC (12). If TVC is high and if a given regional vascular conductance comprises a large fraction of TVC, then changes in conductance in this regional vascular bed can contribute more to blood pressure regulation than if that regional vascular conductance is low. HVC constituted $19.7 \pm 0.9\%$ of TVC at rest and $33.5 \pm 2.6\%$ during heavy exercise. Thus, accordingly, HVC could make a greater contribution to blood pressure regulation during heavy exercise than at rest. Indeed, HVC contributed $10.7 \pm 1.4\%$ to the pressor response during carotid sinus hypotension at rest (~ 3.5 mmHg), whereas at the highest workload, changes in HVC made a significantly greater contribution to the pressor response ($24.3 \pm 3.4\%$, ~ 8.5 mmHg). Conversely, if regional vascular conductance does not comprise a large fraction of TVC, then changes in conductance in this regional vascular bed likely contribute less to blood pressure regulation. At rest, RVC constituted $\sim 5\%$ of TVC. This fraction of TVC decreased to $< 1\%$ during heavy exercise. Accordingly, at rest, RVC contributed only $4.0 \pm 0.7\%$ (~ 1.4 mmHg) to the pressor response during carotid sinus hypotension, and at the highest workload, RVC contributed only $1.6 \pm 0.3\%$, which represents < 1 mmHg of the pressor response.

Our data indicate that as workload increased, the contribution of vasoconstriction within the active skeletal muscle to the reflex pressor response to BCO also progressively increased. In dogs at rest, skeletal muscle blood flow accounts for 45% of CO and, therefore, 45% of TVC (6). At rest in our experiments, TVC averaged $42 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, which therefore reflects $19 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ to skeletal muscle and $23 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ to nonskeletal muscle. This latter value includes cardiac vascular conductance, which is $\sim 2.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ at rest (6). Thus vascular conductance to nonmuscle areas is $20.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ at rest. In dogs during exercise, vascular conductance in nonactive areas does not increase (and may decrease); thus all the rise in TVC with increasing workloads reflects vasodilation within the active muscle (including the cardiac vasculature). At the highest workload, TVC decreased by $24 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ in response to BCO. Even if all nonactive areas, including the brain, spinal cord, and kidneys, vasoconstricted completely (e.g., zero blood flow, zero vascular conductance, and infinite vascular resistance), which was not the case (see RVC responses in Fig. 2), the maximal decrease in TVC could only be at most $20.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, which is less than the observed decrease in TVC ($24.1 \pm 4.2 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$) in response to BCO at this workload. Thus we conclude that vasoconstriction within the active skeletal muscle must participate in the pressor response to BCO dur-

ing heavy exercise. Indeed, Fig. 3 shows that the reduction in HVC [of which the vast majority is to skeletal muscle even at rest (6)] plays an increasingly important role in mediating the pressor response to BCO as workload rises. Furthermore, if the response of all skeletal muscle is similar to that of the hindlimb, then we calculate that vasoconstriction within all skeletal muscle (skeletal muscle in the hindlimb and elsewhere) contributes 29% to the pressor response at rest and 61% at the highest workload [calculations based on the known percent contribution of the hindlimb and the known distribution of CO at rest in dogs (5) and the fact that all the increase in TVC with exercise is muscle vasodilation]. Therefore, during heavy exercise, skeletal muscle is the primary target organ for baroreflex-mediated vasoconstriction.

The MAP, HR, and HVC responses to carotid sinus hypotension at rest and during exercise were similar to those described by O'Leary et al. (17). They concluded that since carotid sinus hypotension caused little change in HR during rest or exercise, most of the pressor response was caused by reflex vasoconstriction and not CO. However, they did not measure CO. This is an important consideration, since changes in HR alone may not accurately depict changes in CO (14, 29). Furthermore, they were not able to distinguish the mechanism (CO vs. peripheral vasoconstriction) or the relative contributions of the regional vasoconstriction to the pressor response during carotid sinus hypotension. The present study extends these previous observations by quantifying the relative contributions of CO and active and inactive vascular beds in mediating the reflex pressor response to BCO. On the basis of CO values reported previously for resting and exercising dogs (10, 28), O'Leary and colleagues reported that ~11% of the pressor response to carotid sinus hypotension was due to vasoconstriction in the hindlimb, and during higher workloads, ~59% of the pressor response was attributable to a reduction in HVC. Our conclusions are in agreement with these previous findings; however, the percent contribution of the decrease in HVC to the pressor response during heavy exercise is considerably lower in the present study (24 vs. 59%). A likely explanation for this divergent result is that O'Leary and colleagues may have underestimated CO, and thus TVC, at the higher workload. Since a given change in HVC will have a greater effect on blood pressure regulation when TVC is low than when TVC was high (12), it may not be surprising that we report a lower value when TVC was directly calculated than when it was estimated.

A major point of controversy in the field of neural control of the circulation during exercise has been the existence of "functional sympatholysis." The term functional sympatholysis was coined to express a commonly held view that metabolic vasodilation in active skeletal muscle attenuates neurogenic vasoconstriction (21). Indeed, there are several lines of evidence spanning several decades suggesting a reduced vasoconstrictor response to sympathetic stimulation in contracting skeletal muscle (3, 8, 21, 27). Conversely, a number of

other studies have reported that local metabolic vasodilation in the active skeletal muscle does not override neurogenic vasoconstriction (5, 7, 17, 25, 26). Causes for the disparate results are not entirely clear. However, it has been argued that with the vast differences that exist in baseline blood flow, resistance, and conductance between rest and exercise, opposite conclusions can be drawn on the magnitude of the vasoconstrictor response when the responses are analyzed in terms of resistance vs. conductance or absolute change vs. percent change (12). One limitation with this study and others that examine baroreflex-induced increases in sympathetic nerve activity is that it is unknown whether the rise in sympathetic nerve activity is similar at rest and throughout exercise. However, despite this limitation, our data demonstrate that as workload increases, the active skeletal muscle vascular bed becomes the primary site for carotid baroreflex-induced vasoconstriction.

The pressor response to carotid sinus hypotension in the intact, conscious animal will, in turn, activate a variety of control mechanisms. It is important to note, however, that we wanted to examine the relative contributions of CO and peripheral conductance mediating the pressor response to carotid sinus hypotension under physiological conditions, where the multiple interactions inherent in the feedback control of arterial pressure are intact. It is recognized that the observed hemodynamic changes may be more profound in the absence of the opposing compensatory mechanisms (e.g., after aortic and cardiopulmonary barodenervation).

Summary. This is the first study to quantify the contribution of CO and regional vascular conductances to the carotid baroreflex-mediated increases in MAP at rest and during mild to heavy treadmill exercise. Our data demonstrate that the pressor response to carotid sinus hypotension is mediated via peripheral vasoconstriction. Since TVC is the sum of all regional vascular conductances, we were able to determine the contributions of HVC and RVC to the carotid baroreflex-mediated pressor response. The relative contribution of the hindlimb increased and that of the kidney decreased with increasing workloads. These data suggest that the active skeletal muscle vascular bed and not the renal bed is an important site for carotid baroreflex-induced vasoconstriction to raise and maintain arterial pressure during a hypotensive stimulus. Thus, in response to carotid sinus hypotension, the relative importance of vasoconstriction in active skeletal muscle increases and that in inactive beds (e.g., renal) decreases as exercise intensity rises.

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