

Baroreflex modulation of muscle sympathetic nerve activity during posthandgrip muscle ischemia in humans

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Cui, Jian, Thad E. Wilson, Manabu Shibasaki, Nicole A. Hodges, and Craig G. Crandall. Baroreflex modulation of muscle sympathetic nerve activity during posthandgrip muscle ischemia in humans. *J Appl Physiol* 91: 1679–1686, 2001.—To identify whether muscle metaboreceptor stimulation alters baroreflex control of muscle sympathetic nerve activity (MSNA), MSNA, beat-by-beat arterial blood pressure (Finapres), and electrocardiogram were recorded in 11 healthy subjects in the supine position. Subjects performed 2 min of isometric handgrip exercise at 40% of maximal voluntary contraction followed by 2.5 min of posthandgrip muscle ischemia. During muscle ischemia, blood pressure was lowered and then raised by intravenous bolus infusions of sodium nitroprusside and phenylephrine HCl, respectively. The slope of the relationship between MSNA and diastolic blood pressure was more negative ($P < 0.001$) during posthandgrip muscle ischemia (-201.9 ± 20.4 units·beat⁻¹·mmHg⁻¹) when compared with control conditions (-142.7 ± 17.3 units·beat⁻¹·mmHg⁻¹). No significant change in the slope of the relationship between heart rate and systolic blood pressure was observed. However, both curves shifted during postexercise ischemia to accommodate the elevation in blood pressure and MSNA that occurs with this condition. These data suggest that the sensitivity of baroreflex modulation of MSNA is elevated by muscle metaboreceptor stimulation, whereas the sensitivity of baroreflex of modulate heart rate is unchanged during posthandgrip muscle ischemia.

metaboreceptor; baroreflex sensitivity; heart rate; exercise

EXERCISE IS A POTENT STIMULUS to activate the sympathetic nervous system. Static and dynamic exercise increases arterial blood pressure and heart rate. The increase in heart rate is considered a response to central command associated with exercise, whereas the rise in arterial blood pressure occurs mainly through an increase in cardiac output and peripheral vasoconstriction (24). Increases in muscle sympathetic nerve activity (MSNA) during exercise are caused, reflexively, by stimulation of muscle afferents that are sensitive to metabolites produced within the contracting muscle (12). This concept comes from the observation

that, during postexercise circulatory occlusion, a maneuver that maintains muscle metaboreflex activation while removing central command and muscle mechanoreceptor afferent stimulation, blood pressure, MSNA, and vascular resistance remain elevated (12, 16).

Although the principal control mechanisms that regulate autonomic adjustments to exercise are metaboreflexes, mechanoreflexes, and central command, arterial baroreceptors remain functional in modulating blood pressure during exercise (20). Neurons in the nucleus tractus solitarius, which is an important pathway for the baroreflex (1), receive excitatory inputs from receptors sensitive to metabolites of muscle contraction in rats (31). Moreover, afferent input from arterial baroreceptors is a powerful modulator of sympathoexcitation evoked by metabolically sensitive skeletal muscle receptors (18, 19). Taken together, the aforementioned studies suggest a possible interaction between the metaboreflex and the baroreflex; however, the effects of muscle metaboreceptor stimulation on baroreflex function have not been clearly defined.

Prior studies demonstrate that, during dynamic exercise, the carotid baroreflex response curve resets to higher operating pressures in dogs (33) and in humans (20, 27) without changing the maximum gain of these curves (20, 29). However, these studies did not specifically investigate whether the resetting of the baroreflex curve was due to muscle metaboreceptor stimulation, as opposed to other variables such as central command and mechanoreceptor stimulation, which are known to reset baroreflex curves (14). A number of studies have demonstrated an interaction between the muscle metaboreflex and the baroreflex. For example, arterial baroreflexes were shown to reduce the sensitivity of the muscle metaboreflex in dogs (28). In humans, Eckberg and Wallin (4) showed that decreases in muscle sympathetic nerve activity during carotid baroreceptor stimulation via neck suction was greater during handgrip exercise than during rest, whereas Papelier et al. (17) reported that muscle metaboreflex

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stimulation shifted the carotid sinus baroreflex curve to accommodate the elevation in blood pressure that occurs with static exercise in humans. Finally, Scherrer et al. (27) showed that, during static exercise in humans, arterial baroreflexes (i.e., aortic and carotid baroreflexes) were more effective in buffering reflex sympathetic activation relative to during resting conditions.

Although these studies provide evidence of an interaction between the baroreflex and the metaboreflex with respect to control of blood pressure during exercise and/or postexercise muscle ischemia, they do not identify whether muscle metaboreflex stimulation specifically alters baroreflex control of MSNA. The present study was undertaken to test the hypothesis that muscle metaboreceptor stimulation alters baroreflex control of MSNA and heart rate in humans. To test this hypothesis, baroreflex control of MSNA and heart rate were assessed on a beat-by-beat basis during rapid pharmacologically induced changes in arterial pressure during both resting and posthandgrip muscle ischemic conditions.

METHODS

Subjects. Eleven subjects (8 men, 3 women) participated in this study. The subjects' average age was 34 ± 2 (SE) yr, and all were of normal height (174 ± 3 cm), weight (74 ± 3 kg), and health. A written informed consent from each subject was obtained before participation in these institutionally approved studies.

Measurements. Multifiber recordings of MSNA were made with a tungsten microelectrode inserted in the peroneal nerve in the popliteal fossa. A reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria (32). The nerve signal was amplified (50,000–90,000 times), passed through a band-pass filter with a bandwidth of 500–5,000 Hz, and integrated with a time constant of 0.1 s (Iowa Bioengineering, Iowa City, IA). The mean voltage neurograms were displayed together with blood pressure on a chart recorder. The nerve signal was also routed to an oscilloscope and a loudspeaker for monitoring throughout the study.

Heart rate was obtained from the electrocardiogram signal (SpaceLabs, Redmond, WA) interfaced with a cardi tachometer (CWE, Ardmore, PA). Blood pressure was recorded on a beat-by-beat basis from a finger (Finapres, Ohmeda, Louisville, CO). Resting blood pressures obtained from the Finapres was verified during the experiment by auscultation (SunTech, Medical Instruments, Raleigh, NC). To ensure that subjects avoided Valsalva maneuvers during isometric handgrip, spontaneous respiratory frequency was monitored by using piezoelectric pneumography. Maximal voluntary handgrip contraction was determined in the supine position from the dominant arm using a handgrip dynamometer before data collection. The average from three isometric handgrip attempts was used as the subject's maximal voluntary contraction.

Protocols. All studies were conducted with the subject in the supine position. To assess baroreflex sensitivity, changes in arterial blood pressure were induced by bolus injections of sodium nitroprusside and phenylephrine HCl (3, 7) during both nonexercise and posthandgrip ischemic conditions. This

method unloads and loads, respectively, both the aortic and carotid baroreceptors without causing measurable changes in central venous pressure (2). However, independent contributions from these baroreceptor populations cannot be discriminated with this method.

These drugs were administered intravenously via a catheter placed in the nonexercising arm. For the nonexercise trials, after a 5-min baseline period, 100 μ g of sodium nitroprusside were administered, followed \sim 60 s later by 150 μ g of phenylephrine HCl. These doses decreased arterial pressure 10–15 mmHg below baseline levels and then increased blood pressure 5–10 mmHg above baseline levels, respectively. During resting conditions, three of these challenges were performed separated by 15-min intervals. This duration was sufficient for arterial blood pressure, heart rate, and MSNA to return to predrug levels. Results from these three trials were averaged and are reported as the nonexercise trial (25).

After another rest period, the subjects performed isometric handgrip exercise at 40% maximal voluntary contraction for 2 min. Five seconds before the end of exercise, the circulation to the exercising arm was arrested by rapid inflation of a pneumatic cuff (Hokanson, Bellevue, WA) on the upper portion of the arm to 250 mmHg. This level of arm cuff pressure is sufficient to trap metabolites in the exercising arm. Approximately 10–15 s after the end of handgrip exercise, but with the occlusion cuff still inflated, bolus infusions of sodium nitroprusside and phenylephrine HCl were once again administered using the same time course and doses as were used in the nonexercise trials (Fig. 1). Posthandgrip muscle ischemia was maintained for 2.5 min. After a rest period of \geq 15 min to allow arterial pressure, heart rate, and MSNA to return to preexercise levels, the subject repeated the procedure. Results from these two trials were averaged and are reported as the metaboreceptor-stimulated trial.

Data analysis. Data were sampled at 200 Hz through a commercial data acquisition system (Biopac System, Santa Barbara, CA) and analyzed using LabView software (National Instruments, Austin, TX). Beat-by-beat heart rate was calculated from R-R interval of the electrocardiogram. Beat-by-beat systolic and diastolic blood pressure were obtained from the arterial blood pressure waveform.

The integrated neurogram was normalized by assigning a value of 100 to the largest amplitude of a sympathetic burst during the first minute before the administration of drugs or the onset of exercise. All bursts for that trial were then normalized against that value (7). Taking into account burst latency from the R wave of the electrocardiogram, MSNA bursts were identified by manual inspection of the neurogram. Burst areas of the integrated neurogram and systolic and diastolic blood pressure were measured simultaneously on a beat-by-beat basis. Total MSNA activity of the burst was defined as the burst area of the rectified and integrated neurogram.

The sensitivity of baroreflex control of MSNA was identified from the linear relationship between MSNA and diastolic blood pressure during pharmacologically induced changes in blood pressure (7, 25). Diastolic blood pressure was used because MSNA correlates closely with diastolic blood pressure but not with systolic blood pressure (30). To perform a linear regression between nerve activity and blood pressure, values for MSNA were averaged over 3-mmHg diastolic blood pressure ranges. This pooling procedure reduces the statistical impact of inherent beat-by-beat variability in nerve activity due to nonbaroreflex influences (e.g., respiration) (7). Because MSNA was often completely suppressed when blood pressure exceeded a particular threshold, the relationship between MSNA and blood pressure was frequently nonlinear

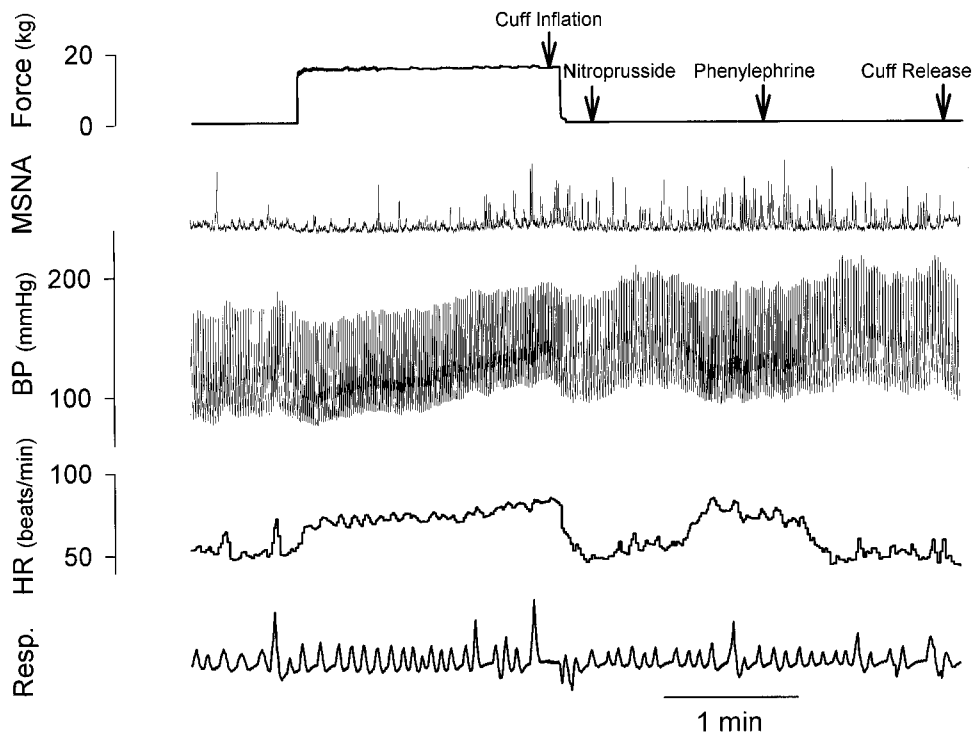


Fig. 1. Representative tracings obtained from 1 subject during handgrip exercise and posthandgrip muscle ischemia (PHGMI). Handgrip force, integrated muscle sympathetic nerve activity (MSNA), blood pressure (BP; via Finapres), beat-by-beat heart rate (HR), and respiration (Resp; via pneumotrace) are shown. The subjects performed isometric handgrip exercise at 40% maximal voluntary contraction for 2 min. Before the end of exercise, a pneumatic cuff on the upper portion of the exercising arm was inflated to 250 mmHg (Cuff Inflation). Approximately 10–15 s after the end of handgrip exercise, HR returned to preexercise levels. A bolus of sodium nitroprusside (100 μ g) was then administered (Nitroprusside), which decreased blood pressure 20–30 s after administration. Phenylephrine HCl (150 μ g) was then administered ~60 s after the administration of sodium nitroprusside (Phenylephrine). Phenylephrine HCl caused an increase in BP 20–30 s after its administration. The cuff was deflated (Cuff Release) 15–30 s after the peak hypertensive response associated with phenylephrine HCl infusion. Arrows on the force tracing indicate the aforementioned events for this subject.

at high blood pressures. In the present analysis, only the linear part of the data was used to estimate the slope of relationship between MSNA and diastolic blood pressure (see Fig. 2).

Baroreflex modulation of heart rate was identified from the relationship between beat-by-beat heart rate and systolic blood pressure during pharmacologically induced changes in blood pressure. Beat-by-beat heart rates were also pooled over 3-mmHg systolic blood pressure ranges, followed by linear regression analysis between heart rate and systolic blood pressure.

Statistical analyses were performed using commercially available software (StatView 5.0). Differences in hemodynamic responses within nonexercise trials or exercise trials were evaluated using a repeated-measures one-way ANOVA. Differences between pharmacologically induced responses during nonexercise and posthandgrip muscle ischemia trials were evaluated with a repeated-measures two-way ANOVA. The effects of posthandgrip muscle ischemia on baroreflex gains were compared with the nonexercise trials via paired *t*-tests. All values are reported as means \pm SE. *P* values < 0.05 were considered statistically significant.

RESULTS

Recordings of handgrip force, integrated MSNA, blood pressure, instantaneous heart rate, and respiration during handgrip and posthandgrip muscle ischemia for a representative subject are shown in Fig. 1. Hemodynamic and MSNA responses during bolus administration of sodium nitroprusside and phenylephrine HCl during nonexercise trials are shown in Table 1. Hemodynamic responses, as well as MSNA, during preexercise baseline, posthandgrip muscle ischemia, and muscle ischemia plus drug administrations are illustrated in Table 2. There were no significant differences ($P > 0.05$) between hemodynamic parameters

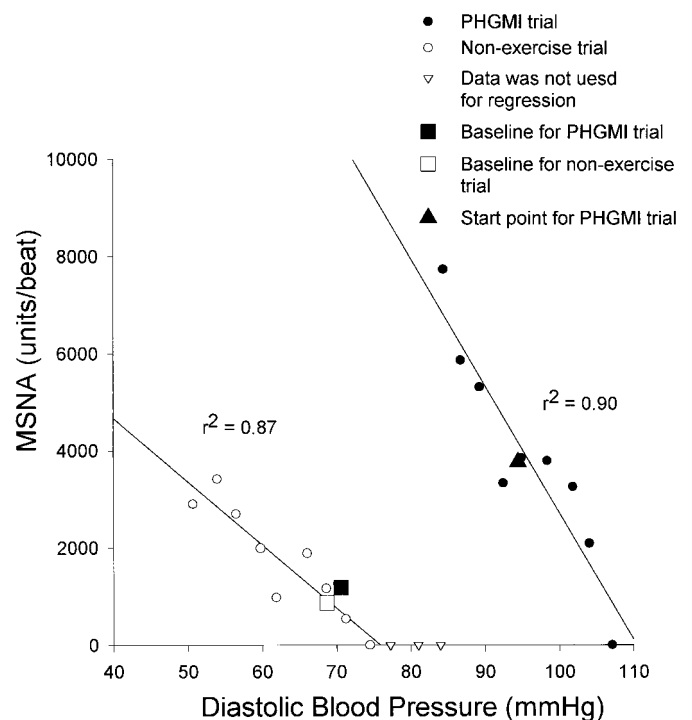


Fig. 2. An example of the linear regression between MSNA and diastolic blood pressure (DBP) for a representative subject. Only the linear portion of the data was used for the linear regression analysis during both rest (\circ) and PHGMI (\bullet) trials. Baseline MSNA and DBP were similar before drug infusion for the nonexercise trial (\square) relative to before handgrip exercise (\blacksquare). PHGMI increased both MSNA and DBP as indicated by a shift in the operating point immediately before infusion of the first drug (\blacktriangle ; starting point for PHGMI trial) relative to the period before the onset of exercise (\blacksquare). Finally, it is clear that the slope relating the change in MSNA relative to the change in DBP is elevated during PHGMI. ∇ , Data that were excluded from the linear regression analysis.

Table 1. SBP, DBP, heart rate, and total activity of MSNA during nonexercise trials

	Baseline	Sodium Nitroprusside	Phenylephrine HCl
SBP, mmHg	125.3 ± 3.4	109.5 ± 5.4*	135.4 ± 4.5†
DBP, mmHg	67.8 ± 1.7	54.5 ± 2.1*	72.4 ± 2.4†
Heart rate, beats/min	53.6 ± 1.5	72.8 ± 2.5*	47.5 ± 1.2*†
MSNA × 10 ³ units/min	39.5 ± 6.8	161.7 ± 16.5*	17.1 ± 3.7†

Values are means ± SE for 11 subjects. The data for baseline are values of ~1 min before the infusion of sodium nitroprusside; the data for nitroprusside are mean values of ~15 s during lowest blood pressure induced by sodium nitroprusside; and the data for phenylephrine HCl are mean values of ~15 s during highest blood pressure induced by phenylephrine HCl. SBP, systolic blood pressure; DBP, diastolic blood pressure; MSNA, muscle sympathetic nerve activity. * $P < 0.05$ compared with baseline. † $P < 0.05$ compared with sodium nitroprusside.

before the onset of handgrip exercise (Table 2) relative to the period before drug administration for the nonexercise trial (Table 1). Posthandgrip muscle ischemia significantly elevated MSNA and systolic and diastolic blood pressure, whereas heart rate returned to preexercise levels (Table 2). Changes in blood pressure and heart rate induced by sodium nitroprusside and phenylephrine HCl during posthandgrip muscle ischemia were similar with those during the nonexercise trial ($P = 0.93$ for systolic blood pressure, $P = 0.46$ for diastolic blood pressure, $P = 0.33$ for heart rate, 2-way ANOVA). Breath holding was not observed in any subjects during these procedures.

An example of the linear regression between MSNA and diastolic blood pressure for a representative subject is shown in Fig. 2. The slope of the relationship between MSNA and diastolic blood pressure was more negative when baroreflexes were perturbed in combination with muscle metaboreceptor stimulation relative to the nonexercise trial (posthandgrip muscle is-

Table 2. SBP, DBP, heart rate, and total activity of MSNA before handgrip and during posthandgrip muscle ischemia trial

	Baseline	PHGMI	Sodium Nitroprusside	Phenylephrine HCl
SBP, mmHg	127.7 ± 2.7	154.3 ± 4.9*	139.9 ± 6.9†	165.1 ± 5.2*‡
DBP, mmHg	67.5 ± 1.7	85.3 ± 2.4*	73.1 ± 2.7†	88.9 ± 1.8*‡
Heart rate, beats/min	54.7 ± 1.4	55.4 ± 1.8	75.9 ± 2.5*†	52.3 ± 2.3‡
MSNA × 10 ³ units/min	35.0 ± 7.5	109.6 ± 15.7*	255.9 ± 20.6*†	80.1 ± 18.2*‡

Values are means ± SE for 11 subjects. The data for baseline are mean values of ~1 min before the onset of handgrip exercise. The data for posthandgrip muscle ischemia (PHGMI) are mean values of ~15 s during arm occlusion and just before the fall in blood pressure induced by sodium nitroprusside; the data for sodium nitroprusside are mean values of ~15 s during lowest blood pressure induced by sodium nitroprusside during PHGMI; the data for phenylephrine HCl are mean values of ~15 s during the highest blood pressure induced by phenylephrine HCl during PHGMI. * $P < 0.05$ compared with baseline. † $P < 0.05$ compared with PHGMI. ‡ $P < 0.05$ compared with sodium nitroprusside.

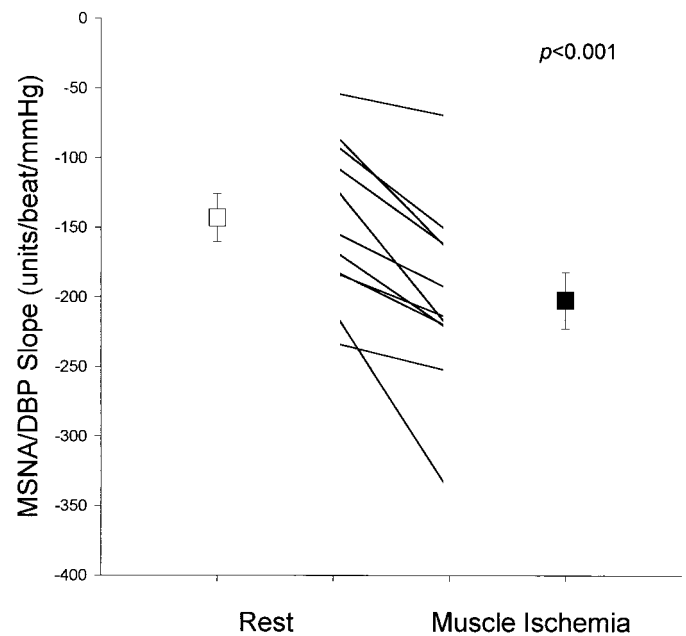


Fig. 3. Change in the slopes from the linear regression between MSNA and DBP for each subject (lines; $n = 11$) as well as mean slopes (\pm SE) from rest to muscle ischemic conditions. Muscle ischemia significantly elevated (i.e., more negative) the average slope (\blacksquare) between the change in MSNA relative to the change in DBP than that during rest condition (\square).

chemia: -201.9 ± 20.4 , nonexercise: -142.7 ± 17.3 units·beat⁻¹·mmHg⁻¹; $P < 0.001$; Fig. 3). Metaboreceptor stimulation significantly shifted the relationship between diastolic blood pressure and MSNA upward and to the right (see Fig. 1) as evidenced by a significant increase in blood pressure and MSNA during posthandgrip muscle ischemia before drug administration (see Table 2). These results indicated that muscle metaboreceptor stimulation reset baroreflex modulation of MSNA and increased the sensitivity of baroreflex control of MSNA.

An example of the linear regression between heart rate and systolic blood pressure for a representative subject is shown in Fig. 4. Although the slope of the relationship between heart rate and systolic blood pressure was similar ($P = 0.79$) for posthandgrip muscle ischemia (-0.846 ± 0.079 beats·min⁻¹·mmHg⁻¹) and nonexercise trials (-0.821 ± 0.09 beats·min⁻¹·mmHg⁻¹, Fig. 5), the curve expressing this relationship was shifted to the right during posthandgrip muscle ischemia as evidenced by an increase in blood pressure without a corresponding change in heart rate (see Fig. 4 and Table 2). This finding indicates that stimulation of muscle metaboreceptors shifts baroreflex regulation of heart rate to accommodate the elevation in blood pressure that accompanies posthandgrip muscle ischemia.

DISCUSSION

The main finding of the present study is that the slope of the relationship between MSNA and diastolic blood pressure during posthandgrip muscle ischemia

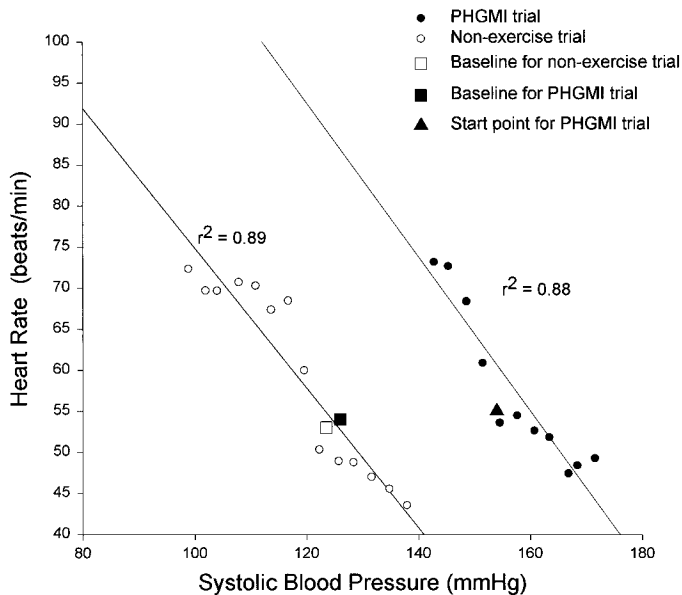


Fig. 4. An example of the linear regression between HR and systolic blood pressure (SBP) for a representative subject. PHGMI shifted the regression line representing the change in HR relative to SBP to the right. However, the slope of this relationship was unaltered during PHGMI. Symbols are as described in Fig. 2.

was more negative relative to the resting condition. Moreover, posthandgrip muscle ischemia reset the baroreflex curve expressing the relationship between diastolic blood pressure and MSNA upward and to the right. These findings suggest that the sensitivity of baroreflex control of MSNA in humans is elevated and the baroreflex curve is reset when muscle metaboreceptors are stimulated. In contrast, this same perturbation shifts baroreflex control of heart rate to high blood pressures but does not alter the sensitivity of this reflex.

Blood pressure and MSNA were elevated during posthandgrip muscle ischemia in the present experiment. It has long been recognized that MSNA increases during isometric exercise and during postexercise muscle ischemia (12, 26). The increase in MSNA during postexercise muscle ischemia is caused by stimulation of muscle afferents, which are sensitive to metabolites of the contracting muscle (12).

In the present study, baroreflex modulation of MSNA was assessed by calculating the slope of total activity of MSNA to diastolic blood pressure on a beat-by-beat basis. This relationship has been used extensively to probe the role of the baroreflex in humans. Intravenous bolus injections of vasoactive substances (e.g., sodium nitroprusside and phenylephrine HCl) have also been widely used to assess baroreflex responsiveness (3, 7, 15, 25). The dose and time course for the administration of vasoactive drugs in the present experiment were the same as those in previous studies (7, 25). As expected, sodium nitroprusside-induced decreases in blood pressure resulted in significant elevations in MSNA. Conversely, increases in blood pressure due to phenylephrine HCl infusion caused significant decreases in MSNA. However, during postexercise

muscle ischemia, phenylephrine HCl-induced increases in blood pressure did not return MSNA to levels similar to, or less than, MSNA before exercise. This observation suggests baroreceptor-mediated suppression of MSNA was insufficient to completely overcome metaboreceptor-mediated activation of MSNA (see Table 2).

Prior studies have demonstrated an interaction between baroreflexes and metaboreflexes. For example, the arterial baroreflex opposes the rise in blood pressure during exercise (33) and reduces the sensitivity of the muscle metaboreflex in dogs (28). Less clear, however, is the effect of the muscle metaboreflex on baroreflex regulation of arterial blood pressure.

During dynamic exercise, carotid sinus baroreflex response curves reset to higher operating pressures in dogs (33) and in humans (17, 20, 27). However, the gain of the response under these conditions was unaffected by dynamic exercise (20, 29). Moreover, Fadel et al. (5) recently reported that the gain of carotid baroreflex control of MSNA was unaltered during dynamic exercise. The rationale for the lack of change in baroreflex gain during dynamic exercise, in context to the present findings in which muscle metaboreceptor stimulation increased the baroreflex gain, may be related to the fact that, during dynamic exercise, central command, muscle metaboreflexes, and muscle mechanoreflexes all likely contribute to hemodynamic responses.

Other studies suggest that baroreflex control of MSNA might be changed during static exercise. Eckberg and Wallin (4) showed that, during isometric handgrip exercise, carotid baroreflex control of MSNA was attenuated during the hypotensive stimulus by neck pressure and was elevated during the hyperten-

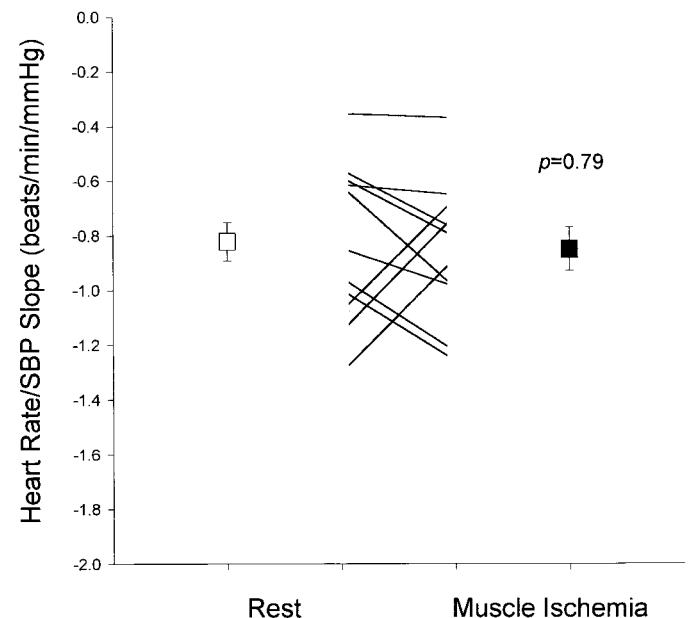


Fig. 5. Change in slopes from the linear regression between HR and SBP for each subject (lines; $n = 11$) as well as mean slopes (\pm SE) from rest (\square) to muscle ischemic (\blacksquare) conditions. Muscle ischemia did not alter the sensitivity of baroreflex control of HR.

sive stimulus by neck suction. Moreover, Scherrer et al. (27) found that partial pharmacological suppression of the rise in blood pressure during static handgrip (via sodium nitroprusside infusion) augmented the exercise-induced increase in MSNA by 300%, whereas pharmacological accentuation of the exercise-induced elevation in blood pressure (via phenylephrine HCl infusion) attenuated the elevation in MSNA by >50%. Their results indicate that the arterial baroreflex during static exercise is more effective in buffering the reflex sympathetic activation, relative to during resting conditions. Although the aforementioned results suggest that baroreflex control of MSNA is changed during isometric handgrip exercise, in those studies the effects of the metaboreflex could not be separated from contributions from central command and muscle mechanoreflexes. To focus specifically on the interaction between the metaboreflex and baroreflex, Papelier et al. (17) estimated carotid stimulus response curves by positive and negative neck pressure during leg occlusion after dynamic leg exercise (e.g., cycle ergometry). They found that postexercise ischemia increased the gain of carotid baroreflex control of blood pressure during the hypotensive stimulus and reduced the gain of carotid baroreflex control of blood pressure during the hypertensive stimulus. However, in that study, the contribution from extracarotid baroreceptors in modulating blood pressure during muscle metaboreceptor stimulation was not addressed. In contrast, in the present investigation, the effects of loading and unloading both aortic and carotid baroreceptors on the control of MSNA and heart rate during posthandgrip muscle ischemia were investigated. We found that the slope of the change in total activity of MSNA relative to the change in diastolic blood pressure was more negative during posthandgrip muscle ischemia. Thus arterial baroreflex control of MSNA was significantly elevated by factors associated with metaboreceptor stimulation.

Compared with the nonexercise condition, baroreflex control of heart rate was shifted to high blood pressures, but the sensitivity of this reflex was unaffected by muscle metaboreceptor stimulation. This finding is consistent with findings from previous studies (10, 17). A possible explanation for the maintenance of the sensitivity of baroreflex modulation of heart rate during muscle metaboreceptor stimulation, compared with MSNA responses, may be related to an absence of an interaction between muscle metaboreceptor stimulation and baroreflex control of cardiac vagal activity. Thus baroreflex control of cardiac vagal activity may be unaffected by muscle metaboreceptor stimulation. This argument is strengthened by findings from Iellamo et al. (10), who suggest that the return of heart rate to preexercise levels during postexercise muscle ischemia is due to baroreflex-mediated increases in cardiac parasympathetic outflow that "overpower" metaboreceptor-mediated increases in cardiac sympathetic outflow.

Study limitations. It has been well documented that pressor responses to muscle ischemia are independent of pain associated with muscle ischemia (6, 23). For

example, Freund et al. (6) found that blood pressure responses during postexercise muscle ischemia were similar after withdrawal of painful sensations by gradual sensory nerve blockade. Nevertheless, we cannot exclude the possibility that differences in baroreflex slopes between nonexercise and muscle ischemic trials in the present experiment were related to increased perception of pain during the muscle ischemic trial. However, we are unaware of any data demonstrating that baroreflex modulation of MSNA is altered by the perception of pain.

Previously, McClain et al. (13) showed that circulatory occlusion of a resting arm does not increase MSNA or blood pressure. Similar findings were reported by Iellamo et al. (9) in which circulation occlusion of the thigh without prior exercise did not significantly affect blood pressure, pulse interval, or sensitivity of baroreflex control of sinus node. Given these findings, it is unlikely that potential stimulation of muscle mechanoreceptors associated with arm occlusion contributed to the observed responses in the present study. However, Haouzi et al. (8) demonstrated that vascular bed distension, induced pharmacologically or by venous occlusion, could increase the discharge rates of group III and IV muscle afferents in cats. Moreover, Rotto et al. (22) showed that the products of metabolism could sensitize group III muscle afferents to static contraction in cats. Therefore, we cannot exclude the possibility that group III and IV afferents, activated by a combination of cuff inflation and metaboreceptor stimulation, might have contributed to altered baroreflex responses during posthandgrip muscle ischemia.

In the present study, the sensitivity of baroreflex control of MSNA was estimated from the slope of the relationship between MSNA and diastolic blood pressure. The relationship of MSNA and diastolic blood pressure is likely sigmoidal across a wide range of blood pressures. In the present study, relatively small changes in diastolic blood pressure occurred during the pharmacological intervention. Moreover, we only used the linear portion of the data to identify the slope of the relationship between MSNA and diastolic blood pressure (see Fig. 2). Thus we do not know whether metaboreceptor stimulation alters the maximal gain of baroreflex control of MSNA. We can, however, conclude that factors associated with metaboreceptor stimulation increase baroreflex control of MSNA within a diastolic blood pressure range of approximately ± 15 mmHg around the operating point.

The basic premise of the present study was that without pharmacologically induced changes in blood pressure, MSNA would have remained constant during the period of posthandgrip muscle ischemia. This premise is supported by findings from Ray et al. (21), who demonstrated that MSNA does not change between the first and second minute of posthandgrip muscle ischemia. Therefore, it is doubtful that increased baroreflex modulation of MSNA during the period of ischemia was affected by baroreflex independent changes in MSNA.

Perspective. The present results suggest that metaboreceptor afferents alter central nervous system control of sympathetic outflow to muscle. Resetting of the baroreflex curve, in combination with a change in the slope of the curve, may indicate that metaboreceptor stimulation alters baroreflex modulation of sympathetic outflow to muscle through activation of both baroreflex-independent and baroreflex-dependent neuronal pools as suggested by Korner (11). The benefits of elevated baroreflex control of MSNA during muscle metaboreceptor stimulation can only be speculated upon at this time. During exercise, the maintenance of elevated blood pressure is required to adequately perfuse the exercising muscle, and the muscle metaboreflex contributes to this elevation in blood pressure. A heightened sensitivity of baroreflex control of MSNA during metaboreceptor stimulation may result in finer control of blood pressure during exercise. Finer control of blood pressure will serve to better maintain blood pressure during challenges that may shift the operating point away from an ideal blood pressure (i.e., set point) for a particular exercise workload.

Conclusion. Results from this study suggest that muscle metaboreceptor stimulation during posthand-grip muscle ischemia reset baroreflex control of MSNA and heart rate to accommodate the elevation in blood pressure exhibited during the ischemic period. Moreover, the sensitivity of baroreflex modulation of MSNA is elevated by muscle metaboreceptor stimulation. These responses may allow for finer control of blood pressure due to muscle metaboreceptor stimulation during exercise.

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