Muscle metaboreflex modulates the arterial baroreflex
dynamic effects on peripheral vascular conductance in humans

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Ichinose, Masashi, and Takeshi Nishiyasu. Muscle metaboreflex modulates the arterial baroreflex dynamic effects on peripheral vascular conductance in humans. Am J Physiol Heart Circ Physiol 288: H1532–H1538, 2005. First published December 2, 2004; doi:10.1152/ajpheart.00673.2004.—We aimed to investigate the interaction between the arterial baroreflex and muscle metaboreflex (as reflected by alterations in the dynamic responses shown by leg blood flow [LBF; by the ultrasound Doppler method], leg vascular conductance [LVC], mean arterial blood pressure [MAP], and heart rate [HR]) in humans. In 12 healthy subjects (10 men and 2 women), who performed sustained 1-min handgrip exercise at 50% maximal voluntary contraction followed immediately by an imposed postexercise muscle ischemia (PEMI), 5-s periods of neck pressure (NP; 50 mmHg) or suction (NS; −60 mmHg) were used to evaluate carotid baroreflex function both at rest (Con) and during PEMI. First, the decreases in LVC and LBF and the augmentation of MAP elicited by NP were all greater during PEMI than in Con (ΔLVC, −1.2 ± 0.2 vs. −1.9 ± 0.2 ml·min⁻¹·mmHg⁻¹; ΔLBF, −97.3 ± 11.2 vs. −177.0 ± 21.8 ml·min⁻¹; ΔMAP, 6.7 ± 1.2 vs. 11.5 ± 1.4 mmHg, Con vs. PEMI; each P < 0.05). Second, in Con, NS significantly increased both LVC and LBF (ΔLVC, 0.9 ± 0.2 ml·min⁻¹·mmHg⁻¹; ΔLBF, 46.6 ± 9.8 ml·min⁻¹; significant change from baseline: each P < 0.05), and, whereas during PEMI no significant increases in LVC and LBF occurred during NS itself (ΔLVC, 0.2 ± 0.1 ml·min⁻¹·mmHg⁻¹; ΔLBF, 10.8 ± 9.6 ml·min⁻¹; each P > 0.05), a decrease was evident in each parameter at 5 s after the cessation of NS. Third, during PEMI, the decrease in MAP elicited by NS was smaller (ΔMAP, −8.4 ± 1.0 vs. −5.8 ± 0.4 mmHg, Con vs. PEMI; P < 0.05), and it recovered to its initial level more quickly after NS (vs. Con). Finally, however, the HR responses to NS and NP were not different between PEMI and Con. These results suggest that during muscle metaboreflex activation in humans, the arterial baroreflex dynamic effect on peripheral vascular conductance is modulated, as exemplified by 1) an augmentation of the NP-induced LVC decrease, and 2) a loss of the NS-induced LVC increase.

skeletal muscle metaboreflex; carotid baroreflex; exercise

DURING HEAVY EXERCISE, the arterial baroreflexes and the reflexes evoked by activation of those afferent nerve endings in the working skeletal muscles that are sensitive to metabolic changes (the so-called muscle metaboreflex) are hypothesized to be activated and, moreover, to interact in ways that lead to modulation of the primary cardiovascular reflex responses (6–9, 15, 19, 20, 24, 25, 29, 31). Two types of interaction between these reflexes have been demonstrated to lead to such modulation. In the first type, the arterial baroreflexes act to oppose the pressor response elicited via the muscle metaboreflex (15, 19, 29, 31). Evidence for this effect has been obtained during dynamic exercise in dogs (31) as well as during static handgrip exercise (29) and postexercise muscle ischemia (PEMI) in humans (15). The second type of interaction involves a modulation of arterial baroreflex function during muscle metaboreflex activation (6–9, 20). However, these interactions (especially the second: viz. modulation of arterial baroreflex function by the muscle metaboreflex) and their consequences are not fully understood.

Papelier et al. (20) found that during PEMI-induced muscle metaboreflex activation, the carotid sinus baroreflex (CBR) displayed a reduced sensitivity to loading [neck suction (NS)] and an enhanced sensitivity to unloading [neck pressure (NP)] in terms of blood pressure regulation but an unchanged sensitivity in terms of heart rate (HR) regulation. The sensitivity of the control exerted by the arterial baroreflexes (carotid and aortic baroreflexes together) over muscle sympathetic nerve activity (MSNA) has been shown to be elevated during both static handgrip exercise and PEMI (8, 9). Very recently, Ichinose et al. (6) reported that the modification of the arterial baroreflex control of MSNA that is seen during PEMI could be a consequence of a muscle metaboreflex-induced alteration in the baroreflex control of both the occurrence and strength of MSNA bursts. Furthermore, a previous study by our laboratory (7) showed that during PEMI (in comparison with the supine rest situation) 1) both the MSNA and mean arterial blood pressure (MAP) responses to NP were augmented, and 2) the period of MSNA depression induced by NS was shortened, and the decrease in MAP was smaller and shorter lasting. From these previous results, we thought that the CBR regulation of peripheral vascular conductance might be modulated by the muscle metaboreflex. However, it is difficult to predict the responses of the intact peripheral vasculature from MSNA data. Because control of peripheral vascular conductance comprises a major element of blood pressure regulation, a direct demonstration of a metaboreflex-induced modification of CBR-mediated vascular regulation is needed for a proper understanding of the interaction between arterial baroreflexes and muscle metaboreflexes. However, an investigation has never been conducted in humans to determine whether and to what extent muscle metaboreflex activation leads to a modulation 1) of the CBR regulation of peripheral vascular conductance, and 2) of CBR dynamic responses (7), which can be evaluated by examining the time course of the CBR-induced alterations in peripheral vascular conductance, MAP, and HR.

Hence, we performed the present study to test the hypothesis that CBR dynamic effects on leg vascular conductance (LVC), leg blood flow (LBF), and MAP are modulated during the
PeMi-induced activation of the muscle metaboreflex in humans. Moreover, we examined the time course of the changes in peripheral vascular conductance induced by CBR in humans, because this is itself not fully understood. To accomplish these ends, we measured the beat-by-beat changes in LBF evoked by neck stimuli (NP or NS) using Doppler ultrasound. This facilitated the measurement of transient, yet marked, changes in peripheral vascular conductance.

Methods

Subjects. We studied 12 healthy volunteers (10 men and 2 women) with a mean age of 24 ± 1 yr, a body weight of 63.9 ± 2.5 kg, and a height of 173.1 ± 1.2 cm. None of the subjects was receiving medication and none smoked. The study, which was in accordance with the Declaration of Helsinki, was approved by the Human Subjects Committee of the University of Tsukuba, and each subject gave informed written consent.

Protocol. After entering the test room, which was maintained at 25°C, each subject adopted the supine position. He or she then performed a maximum voluntary contraction (MVC) with each hand, using a handgrip dynamometer, to allow us to determine 50% MVC. After this, one rapidly inflatable cuff for arterial occlusion was placed on the upper arm (for the production of PeMi) and another on the ankle ipsilateral to the femoral artery used for blood flow measurements (see below). The neck chamber and respiratory mask were fitted. A rest period of at least 15 min was then allowed before data collection began.

The subject was instructed to maintain a constant rate of breathing throughout the experiment, with auditory signals being supplied to assist the subject in controlling breathing frequency at 7.5 cycles/min. The CBR control of HR, MAP, LBF, and LVC was assessed with the use of 5-s periods of NP (50 mmHg) or NS (−60 mmHg). To minimize the respiratory-related modulation of HR and MAP, each neck chamber stimulus (NP or NS) was applied during a voluntary apnea (breathhold) at end-expiration. Throughout each study period (about 12 min), the occlusion cuff placed on the ankle was kept inflated at suprasystolic pressure (−240 mmHg) to impede the foot circulation. The foot has a rich skin vasculature, including arteriovenous anastomoses, which can be affected by changes in the level of arousal (which might be induced by NP and NS in the present study), whereas CBR itself has been reported to have little effect on the circulation in the distal portions of the extremities (3, 4). Thus circulatory arrest in the foot should highlight the primary LVC and LBF responses elicited by CBR.

While the subject was at rest, both types of neck chamber stimulus were applied. After a rest interval of about 2 min, the subject then performed a 60-s period of isometric handgrip exercise at 50% MVC with visual feedback of the achieved force through an oscilloscope display. Five seconds before the cessation of the static handgrip, the occlusion cuff placed on the upper arm was inflated to suprasystolic pressure (−240 mmHg). The cuff remained inflated to produce a 4- to 5-min period of PeMi, and during this period the neck chamber stimuli were applied again, starting more than 30 s after the cessation of the exercise (a time at which we had confirmed that all the measured variables had become stable). Once all the required neck chamber stimuli had been applied, the upper arm cuff was deflated. The same protocol was then performed with the other arm, with the left-right order being randomized. In the course of the experiment on a given arm, two episodes each of NP and NS were delivered at rest and again during PeMi.

NP and NS. A Silastic neck chamber (32) was used to load and unload the carotid baroreceptors. The chamber encased the front half of the neck, with an airtight seal being made between the mandible and the clavicles and sternum. One part of the chamber was connected to a blower device that could apply either suction or pressure to left and right carotid regions simultaneously. Carotid baroreceptor activity was changed as abruptly as possible by applying 5 s of NP (50-mmHg pressure) or 5 s of NS (60-mmHg suction) via the neck chamber. Neck chamber pressure was measured using a pressure transducer mounted on the chamber. Each individual stimulus lasted 5 s, and the interstimulus interval was 30 s. The order of these stimuli was randomized. The neck chamber stimuli were applied under the control of a computer-operated system in which changes in chamber pressure were triggered by the first R wave occurring 3 s or more after the beginning of the breathhold (to minimize the respiratory-related modulation of HR and MAP, all neck chamber stimuli were delivered during breathholding). One to two breathing cycles before the beginning of the voluntary apnea, an investigator signaled to the subject to start breathholding at the end of the next normal expiration (i.e., without changing the pattern of breathing until the breathhold itself). The total duration of the voluntary apnea was about 13 s (a 3-s prestimulus period, a 5-s stimulus, and a 5-s poststimulus period). To assess the effect of the apnea itself, measurements were repeated during breathholding but with neck chamber pressure kept at ambient pressure. In each subject, four episodes of each NP and NS and four episodes of apnea alone were examined at rest and again during PeMi.

Measurements. HR was monitored via a three-lead electrocardiogram. Beat-to-beat changes in blood pressure were assessed by finger photoplethysmography (Finapres 2300, Ohmeda). The monitoring cuff was placed around the middle finger with the forearm and hand supported so that the cuff was aligned at heart level. The subject wore a mask connected to a respiratory flowmeter (RF-H, Minato Medical Science) for the measurement of respiratory flow.

An ultrasound Doppler system (HDI 3500, ATL Ultrasound) equipped with a transducer probe (model L12-5) with an operating frequency of 6 MHz was utilized to simultaneously measure two-dimensional femoral artery diameter and blood velocity. All measurements were performed with the hand-held transducer probe positioned over the common femoral artery 2–3 cm distal to the inguinal ligament. All Doppler data were recorded continuously on S-VHS videotape (ST-120, Maxell). The videotape record of vessel image obtained during each NP, NS, or apnea trial was digitized using a digital video board (PCI-1411, National Instruments) and stored in a personal computer (ThinkPad T30, IBM) equipped with a computer program for vessel diameter measurement. The femoral artery diameter related to systole (Ds; mm) and that related to diastole (Dd; mm) were taken as the largest diameter and the smallest diameter within each cardiac cycle, respectively. The mean diameter (Dm; mm) was calculated as follows:

\[ D_m = D_s/3 + 2 \cdot D_d/3 \]

The cross-sectional area of the femoral artery (CSAFA; cm²) was estimated as follows:

\[ CSAFA = (D_m/10)^2 \cdot \pi \]

Our finding was that CSAFA was not different between the control and PeMi situations nor was there any significant change during apnea itself or during 5-s periods of NP or NS. The values obtained for femoral artery diameter in trials involving NP and NS are shown in Fig. 1.

Instantaneous mean blood velocity (MBV) was estimated by means of a computer program developed with the aid of LabView (version 6.0, National Instruments). The processes used in the calculation of MBV are outlined below. The frequency spectrum of the analog audio output signal of our ultrasound Doppler unit robustly reflects the Doppler shift frequency spectrum within the audio range (7.5 Khz in this study). The analog audio output signal was digitized at a sampling frequency of 20 Khz through an analog-to-digital converter (DAQ-Card-6062E, National Instruments) for processing by a personal computer equipped with our program. The power spectrum of the
digitized audio signal was obtained using fast Fourier transform analysis techniques, employing a Hanning smoothing window in a 512-data point segment. The mean frequency of the data segment was derived from the spectral data by means of the following formula:

\[
    f_{me} = \frac{\sum_{i=0}^{N/2} (f_i \cdot P_i)}{\sum_{i=0}^{N/2} f_i}
\]

where \( f_{me} \) is mean frequency, \( f_i \) is spectral frequency, \( P_i \) is the power related to the \( f_i \) frequency, and \( N \) is the number of data-points. We then began an analysis of the next data segment of the digitized audio signal [which was advanced 200 data points from the beginning of the previous data segment, so 312 data points (15.6 ms) overlapped]. Our program repeats the above processes in real time and produces 100 values of \( f_{me} \) per second (100 Hz) continuously. The \( f_{me} \) calculated using the above processes correlated very well with the actual mean Doppler shift frequency when the electrically generated arbitrary ultrasound wave was transmitted to the transducer probe and measured using our ultrasound Doppler unit (Fig. 2A). Hence, we regarded \( f_{me} \) as the mean Doppler shift frequency and used it for the calculation of instantaneous MBV (see below). The analog signals representing the ECG, blood pressure waveform, neck chamber pressure, and respiratory flow were digitized at a sampling frequency of 100 Hz and stored together with \( f_{me} \) (thus all data could be analyzed together for the same time period). HR, systolic blood pressure, diastolic blood pressure, MAP, and MBV were calculated by means of an off-line data-analysis program. MBV was derived from the stored \( f_{me} \) data using the following formula:

\[
    \text{MBV} = \frac{f_{me} \cdot C}{2 \cdot f_e \cdot \cos \theta} \cdot 100
\]

where \( f_e \) is the emitted frequency from the transducer probe (6 MHz in our setting), \( C \) is the sound velocity in the tissues (we employed 1,530 m/s), and \( \theta \) is the angle between the blood flow direction and the ultrasound beam (we kept \( \theta \) below 60°). We applied the above formula to all the stored \( f_{me} \) data and obtained an instantaneous MBV profile (Fig. 2B) over the entire measurement period. The instantaneous MBV profile was then integrated over each cardiac cycle to acquire the beat-by-beat velocity-time integral (VTI; cm/beat). LBF was derived from the following formula:

\[
    \text{LBF(ml/min)} = \text{CSA}_{FA}(\text{cm}^2) \cdot \text{VTI(\text{cm/beat})} \cdot \text{HR(\text{beats/min})}
\]

and LVC was calculated as follows:

\[
    \text{LVC} = \text{LBF/MAP}
\]

MBV data were successfully collected in 11 of 12 subjects, and the LBF and LVC data shown here are from those 11 subjects (9 men and 2 women).

**Data analysis.** The assessment of CBR dynamic responses has been described in detail elsewhere (7). Briefly, the 13-s records of MAP, HR, LBF, and LVC obtained during four trials of NP or NS were averaged and integrated over 1-s periods to allow us to assess the time course of the CBR responses. The averaged MAP, LBF, and LVC levels during the 3-s prestimulus period and the HR at 1 s before the stimulus were taken as the baseline values. Because breathholding alone did not cause significant alterations in MAP, HR, LBF, or LVC from these baseline values, the responses of each of the above variables are expressed as the absolute difference from its baseline value. In addition, the peak changes in MAP, HR, LBF, and LVC were averaged for each type of stimulus and are shown as the peak response for each subject.

**Statistical analysis.** Data are presented as means ± SE. For baseline values of LBF, femoral artery diameter, LVC, MAP, and HR and for the peak responses of MAP, HR, LVC, and LBF, comparisons between the control situation and PEMI were made using a Student’s paired t-test. A repeated-measures ANOVA was performed to compare the time course data relating to the HR, MAP, LVC, and LBF responses between the control and PEMI situations. Fisher’s post hoc test was used to assess group mean differences and also to assess differences from the value obtained at 3 s before the application of neck chamber stimuli (i.e., 1 s after the start of breathholding) in the control and PEMI situations. Statistical significance was accepted at a \( P \) value of <0.05.

**RESULTS**

Table 1 shows the baseline values of MAP, HR, LBF, LVC, and femoral artery diameter obtained in the control situation.
and during PEMI. During PEMI, MAP was higher and LVC lower than in control, but HR, LBF, and femoral artery diameter did not differ between the two situations.

**Evoked changes in MAP and HR.** MAP and HR were increased by NP and decreased by NS in both situations (control and PEMI). Figure 3A shows that at 5–10 s after the start of NP (at and after the time at which the peak MAP response occurred), MAP was significantly higher during PEMI than in control.

The time course of the MAP responses to NS differed significantly between control and PEMI (Fig. 4A). In the first 4 s of the MAP response to NS, there were no significant differences between the two conditions. Thereafter, at 5–10 s after the beginning of NS, MAP was significantly higher during PEMI than in control. In addition, the peak MAP response to NS occurred 2–4 s earlier during PEMI than in control.

The time course of the HR responses to neck chamber stimuli (Figs. 3D and 4D) did not differ significantly between control and PEMI.

Table 2 shows the peak MAP and HR responses to each neck chamber stimulus. The peak increase in MAP induced by NP was significantly greater during PEMI than in control, whereas NS induced a significantly smaller decrease in MAP during PEMI than in control. In contrast, the peak changes in HR induced by NP and NS were not significantly different between control and PEMI.

**Evoked changes in LVC and LBF.** LVC and LBF were decreased by NP in both situations (control and PEMI) (Fig. 3, B and C). In control, the first significant decreases in LVC and LBF were observed at 6 and 7 s after the start of NP, respectively, with the peak response occurring at 8–10 s after the onset of NP in both LVC and LBF. During PEMI, LVC and LBF started to decrease at 5 s after the start of NP, and the peak response was reached at 7–10 s after the onset of NP. Over the 5–10 s after the start of NP, LVC was significantly lower during PEMI than in control. At 6–10 s after the start of NP, LBF was significantly lower during PEMI than in control.

The time course of the LVC and LBF responses to NS differed significantly between control and PEMI (Fig. 4, B and C). In control, LVC showed a significant increase from its baseline value throughout the period from 3 to 8 s after the start of NS. A significant increase in LBF from its baseline value was observed at 6 s after the onset of NS. In contrast, during PEMI, 1) neither LBF nor LVC were increased by NS, and 2) LVC was significantly lower than in the control situation at 5–6 s after the start of NS. Furthermore, LVC and LBF each showed a significant decrease from their baseline value at 5 s after the cessation of NS.

The peak LVC and LBF responses to each neck chamber stimulus are summarized in Table 2. The peak decreases in LVC and LBF induced by NP were significantly greater during PEMI than in control, whereas NS induced significantly smaller increases in LVC and LBF during PEMI than in control.

**DISCUSSION**

The major finding made in this investigation was that the dynamic LVC, LBF, and MAP responses mediated by the CBR (as evaluated by analyzing the time course data obtained for the responses to neck chamber stimuli) were modulated during the PEMI-induced activation of the muscle metaboreflex. In detail, the LVC and LBF decreases and MAP increase induced by carotid compression (NP) were greater during PEMI than in the control situation. On the other hand, during PEMI, the LVC and LBF increases elicited by carotid stretch (NS) were diminished, and LVC and LBF were each below the baseline value at 5 s after the cessation of NS. Moreover, the MAP decrease induced by carotid stretch was smaller and shorter lasting during PEMI. Thus our results indicate that the PEMI-induced modulation differs between CBR loading and unloading. Fur-
indexes of the effectiveness of the CBR (2, 11, 18, 33). A several decades, and these responses are regarded as useful distance) responses to NP and NS have been examined over arterial baroreflexes. The net result of the interaction between that reflex and the muscle metaboreflex (Table 1) can therefore be presumed to be decreased LVC actually observed during activation of the control of LVC is modulated. The elevated blood pressure and showing that during muscle metaboreflex activation, the CBR metaboreflex control of both blood pressure and MSNA during muscle activation (6–9, 20). Our results add to this by evidence was provided of modulations of the arterial-baroreflexes oppose the pressor response evoked by the muscle metaboreflex (15, 19, 29, 31). Later, activity, the so-called muscle metaboreflex (1, 13–17, 25, 34). It was demonstrated 10 or more years ago that the arterial baroreflexes oppose the pressor response evoked by the muscle metaboreflex (15, 19, 29, 31). Later, evidence was provided of modulations of the arterial-baroreflex control of both blood pressure and MSNA during muscle metaboreflex activation (6–9, 20). Our results add to this by showing that during muscle metaboreflex activation, the CBR control of LVC is modulated. The elevated blood pressure and decreased LVC actually observed during activation of the muscle metaboreflex (Table 1) can therefore be presumed to be the net result of the interaction between that reflex and the arterial baroreflexes. The characteristics of the vascular conductance (or resistance) responses to NP and NS have been examined over several decades, and these responses are regarded as useful indexes of the effectiveness of the CBR (2, 11, 18, 33). A disadvantage of the use of these stimuli is that because the arterial baroreflex is a closed-loop system, the alteration in arterial blood pressure induced via the carotid sinus baroreceptors will immediately be sensed by the extracarotid sinus baroreceptors (i.e., aortic baroreceptors) and/or other carotid baroreceptors. The resulting secondary reflex effects will tend to counteract the responses evoked via the carotid sinus baroreflex itself (10, 12, 26–28). However, the HR and MAP responses to a brief (5 s) neck chamber stimulus are regarded as being only minimally affected by extracarotid sinus baroreceptors (21, 23). In addition, the use of Doppler ultrasound in the present study provided a noninvasive blood flow measurement with beat-by-beat resolution, and this facilitated measurement of transient, yet marked, changes in vascular conductance. We therefore consider that the LVC responses evoked by our neck chamber stimuli reliably reflect the CBR regulation of LVC (11, 18). Although any HR change induced by NP might alter cardiac output and affect the blood pressure responses (23), neither the HR response nor the time course of the HR change differed between PEMI and the control situation (Fig. 3D). Changes in cardiac stroke volume could also alter the cardiac output; however, previous studies have shown that little change in stroke volume is elicited either by neck chamber stimuli (18) or during PEMI (15). Moreover, according to recent findings by Ogoh et al. (18), the peak MAP response (normally observed at 6–8 s after the start of a 5-s neck chamber stimulus) is mainly due to reflex changes in total vascular conductance, with little contribution being made by any change in cardiac output. Previously, we found that during the PEMI-induced activation of the muscle metaboreflex (using the same protocol as that used here), both the MSNA and MAP responses to NP were augmented (7). In the present study, we directly demonstrated that an augmentation of the LVC response to carotid compression occurred during PEMI. In view of the above considerations, the augmented MAP response to NP seen during PEMI can be attributed to an augmentation of CBR-induced vasoconstriction. Thus our present and previous results suggest that the interaction between the muscle metaboreflex and the CBR leads to an augmentation of the increase in SNA induced by carotid compression, resulting in a greater vasoconstriction and an augmentation of the regulation of blood pressure by the CBR.

Fig. 4. Averaged reflex alterations in MAP (A; n = 12 subjects), LVC (B; n = 11 subjects), LBF (C; n = 11 subjects), and HR (D; n = 12 subjects) elicited by NS in control and PEMI situations. *Significant difference from the baseline value, P < 0.05; †significant difference from the control situation, P < 0.05.

Table 2. Peak MAP, HR, LBF, and LVC responses to NP and NS in control and PEMI situations

<table>
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<tr>
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<th>NP</th>
<th>NS</th>
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<tr>
<td>ΔMAP, mmHg</td>
<td>Control 6.7±1.2</td>
<td>−8.4±1.0</td>
</tr>
<tr>
<td>ΔHR, beats/min</td>
<td>Control 4.4±0.8</td>
<td>−6.6±1.2</td>
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<tr>
<td>ΔLBF, ml/min</td>
<td>Control −97.3±11.2</td>
<td>46.6±9.8</td>
</tr>
<tr>
<td>ΔLVC, ml/min−1·mmHg−1</td>
<td>Control −1.2±0.2</td>
<td>0.9±0.2</td>
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Values are means ± SE. ΔMAP, ΔHR, ΔLBF, and ΔLVC, changes in MAP, HR, LBF, and LVC from baseline values. *Significant difference from control, P < 0.05.
The initial, gradual reduction in MAP that occurs during NS may be due to an altered cardiac output secondary to an HR change (18, 23). In the control situation, the timing of the peak MAP response (which occurred at 5–7 s after the start of NS) showed a delay relative to the peak HR response, but the former occurred at the same time as the peak LVC response. However, during PEMI, the vasodilator response to NS was diminished, and at around the time the peak MAP response was seen in the control situation, MAP was already about halfway back toward its baseline value (recovery to the baseline level was complete at 8 s after the start of NS). At 9–10 s, MAP was above baseline, whereas LVC was significantly below baseline at 10 s, indicating vasoconstriction. In a previous study, we (7) found that during PEMI (compared with control), the period of MSNA depression induced by NS was shortened (NS suppressed MSNA only for the first 1 s) and that subsequently MSNA was rapidly augmented despite the continuation of NS.

Taken together, the above evidence suggests that during PEMI, the shortening of the suppression of SNA induced by carotid stretch would diminish the CBR vasodilator response while the subsequent rapid augmentation of SNA would cause vasoconstriction (as was indeed observed as the last part of the LVC response). These results suggest that during activation of the muscle metaboreflex, 1) the CBR is still capable of suppressing sympathetic nerve activity, but 2) that this effect is insufficient to cause significant leg vascular vasodilation and 3) that the subsequent rapid sympathetic nerve activity augmentation would cause a late vasoconstriction, the result being 4) a smaller decrement in blood pressure and its more rapid recovery.

The unchanged baroreflex regulation of HR during PEMI in this study is consistent with previous reports (7, 8, 20). Because the HR responses to neck chamber stimuli are predominantly mediated by the CBR control of cardiac parasympathetic activity (5), our results suggest that the interaction between the muscle metaboreflex and the arterial baroreflex does not affect the CBR-mediated regulation of cardiac parasympathetic tone. Nishiyasu et al. (15) suggested that cardiac parasympathetic tone would increase during activation of the muscle metaboreflex (i.e., during PEMI) in humans. They suggested that such an increase might form part of the counteraction by the arterial baroreflex of the raised blood pressure induced by the muscle metaboreflex in humans. In view of that and similar suggestions made by others (19, 29, 31), we suggest that during PEMI 1) the arterial baroreflex increases cardiac parasympathetic tone, thus counteracting the blood pressure rise caused by muscle metaboreflex activation; and 2) arterial-baroreflex responsiveness (in terms of the regulation of cardiac parasympathetic activity) is maintained. These two effects would result in there being a higher cardiac parasympathetic tone during PEMI than in the control situation.

It has been reported that during PEMI-induced muscle metaboreflex activation in humans, little change occurs in HR and cardiac output, and thus the increase in blood pressure is due predominantly to peripheral vasoconstriction (1, 6–8, 15–17). In contrast, when the muscle metaboreflex is engaged during dynamic exercise in dogs, large HR and cardiac output responses are observed, and the increase in cardiac output is the major cause of the blood pressure elevation (19, 30, 31, 35). These differences in cardiovascular responses between the two situations raise the possibility that the interaction between arterial baroreflexes and the muscle metaboreflex, and the consequences of this interaction, differ depending on whether the muscle metaboreflex is engaged during the postexercise period (i.e., PEMI) or during dynamic exercise (although we should not ignore the possibility of a species difference). Modulation of arterial baroreflex function by the muscle metaboreflex has been demonstrated during both static handgrip exercise (9) and PEMI (6–8, 20) in humans, but similar studies have never been conducted in humans performing dynamic exercise. Although the present results provide evidence of a modulation of CBR dynamic effects on peripheral vascular conductance during PEMI-induced muscle metaboreflex activation in humans, further studies will be needed before we can fully explain the impact of the interaction between these two reflexes on cardiovascular regulation (i.e., we need data from experiments employing dynamic exercise).

Limitations. One of the limitations of the use of a neck chamber is that it is difficult to quantify transmission of the NP/NS stimuli to the carotid sinus region. Recently, Querry et al. (22) measured the transmission of external pressure (from a neck chamber) to the carotid sinus using a balloon-tipped catheter. They found that 89% of the positive pressure and 82% of the negative pressure was transmitted to the carotid sinus region without a kinetic delay. Furthermore, they showed that neither low-intensity exercise (30% maximal oxygen uptake) nor a Valsalva maneuver significantly affected the transmission of such stimuli. Their results encouraged us to compare responses to NP/NS stimuli between the control and PEMI situations in this study. In our subjects, we did not verify the location of the carotid sinus, which affects the efficacy with which external stimuli are transmitted to the carotid sinus region (22). However, although individual differences in the precise location of the carotid sinus might cause differences among subjects in the responses to the neck chamber stimuli, they should not lead to differences in responses between the two study situations (because there is little possibility of the location of the carotid sinus being much different during PEMI than in control).

In conclusion, the results obtained in this study show that the CBR-induced dynamic changes in LVC, LBF, and MAP are modulated during activation of the muscle metaboreflex in humans. The interaction between the muscle metaboreflex and the arterial baroreflex had the effect of 1) augmenting the LVC, LBF, and MAP responses to NP (baroreceptor unloading), but 2) diminishing the leg vasodilation induced by NS (baroreceptor loading), whereas 3) making the decrease in MAP elicited by NS both smaller and shorter lasting. We suggest that this interaction is one of the mechanisms that helps both to increase blood pressure and to maintain the elevated blood pressure during activation of the muscle metaboreflex.

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REFERENCES


