Muscle metaboreflex activation speeds the recovery of arterial blood pressure following acute hypotension in humans

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Ichinose M, Watanabe K, Fujii N, Kondo N, Nishiyasu T. Muscle metaboreflex activation speeds the recovery of arterial blood pressure following acute hypotension in humans. Am J Physiol Heart Circ Physiol 304: H1568–H1575, 2013. First published March 29, 2013; doi:10.1152/ajpheart.00833.2012.—It has been suggested that the arterial baroreflex and muscle metaboreflex are both activated during heavy exercise and that they interact to modulate primary cardiovascular reflex responses. This proposed interaction and its consequences are not fully understood, however. The purpose of present study was to test our hypothesis that dynamic arterial baroreflex-mediated cardiovascular responses to acute systemic hypotension in humans are augmented when the muscle metaboreflex is active and that this results in a faster recovery of arterial blood pressure. Acute hypotension was induced nonpharmacologically in 12 healthy subjects by releasing bilateral thigh cuffs after 9 min of suprasystolic resting ischemia, with and without muscle metaboreflex activation via postexercise muscle ischemia (PEMI) after 1 min of isometric handgrip exercise at 50% maximum voluntary contraction. The thigh-cuff release evoked rapid reductions in mean arterial pressure (MAP) and increases in heart rate, cardiac output (Doppler), and total vascular conductance (TVC) under control conditions and during PEMI. The reductions in MAP from baseline were greater and the increases in TVC were smaller during PEMI than control. In addition, arterial baroreflex-mediated peripheral vasoconstriction was augmented during PEMI, as evidenced by a near doubling of the rate of recovery of MAP and TVC. These results show that when the muscle metaboreflex is activated in humans, arterial baroreflex-mediated peripheral vasoconstriction elicited in response to acute hypotension is augmented, which halves the time needed for MAP recovery. Such modulation of baroreflex function would be advantageous for maintaining an elevated arterial blood pressure during activation of the muscle metaboreflex.

Both static and dynamic exercise are accompanied by increases in arterial blood pressure, heart rate (HR), and sympathetic nerve activity. It has been hypothesized that these cardiovascular responses are mediated by central command (36), as well as by feedback transmitted via afferent nerves (group III and IV fibers), innervating the working skeletal muscles, which are sensitive to mechanical (the so-called muscle mechanoreflex) and metabolic changes (the so-called muscle metaboreflex) (25, 26, 35) and are modulated via the arterial and cardiopulmonary baroreflexes (35, 36). It is further thought that during heavy exercise, both the arterial baroreflex and muscle metaboreflex are activated and that they interact in ways that lead to modulation of primary cardiovascular reflex responses (7, 13, 15–19, 24, 29, 34, 38, 39, 43). Two types of interaction between the arterial baroreflex and muscle metaboreflex in the control of cardiovascular responses have been demonstrated. In the first, the arterial baroreflex acts to oppose pressor responses elicited via the muscle metaboreflex (29, 38, 39), whereas in the second, arterial baroreflex function is modulated when the muscle metaboreflex is activated (7, 13, 15–19, 24, 34). These interactions (especially the second, viz., modulation of arterial baroreflex function by the muscle metaboreflex) and their consequences are not fully understood, however.

Papelier et al. (34) reported that when the muscle metaboreflex is activated in response to postexercise muscle ischemia (PEMI), the carotid baroreflex exhibited increased sensitivity to unloading (neck pressure) and decreased sensitivity to loading (neck suction), as reflected by changes in arterial blood pressure regulation. In addition, we conducted a series of studies (13, 19) in which we found that during PEMI, carotid baroreceptor unloading evokes greater increases in muscle sympathetic nerve activity (MSNA), peripheral vasconstriction, and arterial blood pressure than are evoked under control conditions. We also found that during PEMI, carotid baroreceptor loading produces a shorter period of MSNA suppression, less vasodilation, and, in turn, smaller reductions in arterial blood pressure. Furthermore, activation of the muscle metaboreflex has been shown to enhance arterial baroreflex sensitivity determined through analysis of the relationship between spontaneous and vasoactive drug-induced changes in arterial blood pressure and MSNA (7, 16–18, 24). These earlier results suggest that when the muscle metaboreflex is activated, arterial baroreflex function is modulated in a way that helps to maintain the elevated arterial blood pressure. However, it remains unknown whether this modulation of baroreflex function contributes to maintaining a higher arterial blood pressure during muscle metaboreflex activation. In addition, the functional importance of the interactions between these two reflexes for arterial blood pressure regulation in the context of systemic hypotension (as opposed to isolated carotid baroreceptor unloading) has never been demonstrated. Indeed, no investigation has ever been conducted to determine whether and to what extent activation of the muscle metaboreflex leads to modulation of dynamic arterial baroreflex-mediated cardiovascular responses to acute systemic hypotension.

Based on the results of the studies mentioned above, we hypothesized that dynamic arterial baroreflex-mediated cardiovascular responses to acute systemic hypotension are augmented when the muscle metaboreflex is activated and that this results in a faster recovery of arterial blood pressure. To test this hypothesis, we used thigh-cuff release after suprasystolic...
METHODS

Subjects. We studied 12 healthy volunteers (10 men and 2 women) with a mean age of 24 ± 1 yr, a body weight of 65.0 ± 1.0 kg, and a height of 173.3 ± 1.4 cm. None of the subjects were receiving medication, and none smoked. The study was carried out in accordance with the Declaration of Helsinki and the code of research activities of Meiji University and was approved by the Human Subjects Committee of the University of Tsukuba. Each subject gave informed written consent.

Procedures. After entering the test room, which was maintained at 25°C, each subject adopted a supine position and then performed a maximum voluntary contraction (MVC) using a handgrip dynamometer held in the right hand. From that measurement we calculated the 50% MVC. Thereafter, rapidly inflatable cuffs were placed on the right upper arm and both thighs for occlusion, and the subject was allowed to rest for at least 15 min before data collection was begun. Each subject participated in two protocols in random order. Protocol 1 started with a 3-min rest period, which was followed by inflation of the thigh cuffs to supersystolic pressure (>240 mmHg) for 9 min. Thigh-cuff pressure rose above systolic blood pressure within <1 s, which prevented significant venous pooling. Seven minutes after the start of the thigh-cuff inflation, the occlusion cuff on the upper arm was inflated to supersystolic pressure for 4 min. This forearm occlusion was done to match the situations in protocols 1 and 2. Immediately after the 9 min, the thigh cuffs were deflated and measurements were continued for an additional 2 min. Protocol 1 was designed to determine the responses under resting control conditions. In protocol 2, resting data were acquired for 3 min, after which the thigh cuffs were inflated for 9 min. Beginning 6 min after the start of the thigh cuff inflation, the subject performed an isometric handgrip exercise for 1 min at 50% MVC. Visual feedback showing the achieved force was provided on an oscilloscope display. Five seconds before cessation of the exercise, the occlusion cuff on the upper arm was inflated to supersystolic pressure. The cuff remained inflated to produce a 4-min period of PEMI. After 2 min of PEMI, which corresponded to 9 min of thigh-cuff inflation, the thigh cuffs were deflated and measurements were continued for an additional 2 min. Protocol 2 was designed to determine the responses during muscle metaboreflex activation. In both protocols, thigh cuff release was initiated at the normal end expiration, as observed from the subject’s diaphragmatic movement. This ensured that all subjects were at the same point in the breathing cycle, which minimized the effects of respiration on the comparison of responses between cuff release trials. After both protocols were finished, we measured aortic diameter under resting conditions, as described in Measurements.

Measurements. HR was monitored using a three-lead electrocardiogram. Beat-to-beat changes in blood pressure were assessed using finger photoplethysmography (Finometer; Finapres Medical Systems, The Netherlands); the monitoring cuff was placed around the middle finger of the left hand, with the forearm and hand supported so that the cuff was aligned at the level of the heart. Occlusion cuff pressures were measured using a pressure transducer mounted on the cuff. We measured cardiac output (CO) using Doppler ultrasound as previously described (28, 30). Briefly, a Doppler ultrasound system (HD1 5000; ATL Ultrasound), equipped with a handheld transducer probe (model D2 CW) with an operating frequency of 2 MHz, was used to continuously measure ascending aortic blood velocity. Aortic diameter was measured in a separate resting session using the same Doppler system with a specific transducer probe (model P3-2) also operating at a frequency of 2 MHz. Our system collects aortic blood velocity at 100 Hz together with the analog signals representing the electrocar-
crease in TVC was smaller during PEMI. The increases in HR, SV, and CO did not differ between the two conditions. When the maximum changes in all of the hemodynamic parameters were expressed as percentages of their baseline values, we found no differences between the two conditions (control vs. muscle metaboreflex activation: ΔMAP, −33.8 ± 2.2%; ΔTVC, 178.0 ± 15.0 vs. 166.7 ± 13.6%; ΔHR, 48.6 ± 4.2 vs. 43.6 ± 2.9%; ΔSV, 38.8 ± 2.2 vs. 41.3 ± 2.8%; and ΔCO, 94.9 ± 7.7 vs. 90.0 ± 5.7%).

Figure 3 shows the AUCs for each hemodynamic parameter during the first minute after thigh-cuff release. The AUCs for MAP, HR, CO, and TVC were significantly smaller during PEMI than in the control condition, which means these parameters recovered more slowly during PEMI than during the control condition.

Table 1. Values of hemodynamic parameters in resting subjects before inflation of thigh cuffs in the control and PEMI trials

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PEMI</th>
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<tbody>
<tr>
<td>MAP, mmHg</td>
<td>76 ± 3.1</td>
<td>78 ± 2.4</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>54 ± 1.9</td>
<td>54 ± 2.0</td>
</tr>
<tr>
<td>SV, ml</td>
<td>96 ± 4.9</td>
<td>96 ± 5.7</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.13 ± 0.21</td>
<td>5.14 ± 0.25</td>
</tr>
<tr>
<td>TVC, ml/min⁻¹·mmHg⁻¹</td>
<td>69.4 ± 4.3</td>
<td>67.0 ± 3.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. PEMI, postexercise muscle ischemia; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TVC, total vascular conductance.

Table 2. Baseline values of hemodynamic parameters in the control and PEMI conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>81 ± 3.2</td>
<td>100 ± 3.5*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>53 ± 2.3</td>
<td>59 ± 2.3*</td>
</tr>
<tr>
<td>SV, ml</td>
<td>97 ± 4.2</td>
<td>89 ± 3.8*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.16 ± 0.26</td>
<td>5.21 ± 0.26</td>
</tr>
<tr>
<td>TVC, ml/min⁻¹·mmHg⁻¹</td>
<td>64.8 ± 4.4</td>
<td>52.7 ± 2.9*</td>
</tr>
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</table>

Values are means ± SE. Baseline values of each hemodynamic parameter were defined by calculating their means during the 30 s immediately before thigh-cuff release. *P < 0.05 vs. control.
eters returned toward baseline faster during PEMI. The AUC for SV also tended to be smaller during PEMI than control ($P = 0.09$), but the difference was not statistically significant.

The slopes of the recoveries of MAP and TVC are shown in Fig. 4. Both slopes were significantly steeper during PEMI than control. Figure 5 shows the amount of time required for MAP recovery from its nadir to 10 mmHg above the nadir and to 50% of its maximum change from the nadir. In the control condition, the 10-mmHg increase in MAP from its nadir took $23.1 \pm 5.1$ s, whereas it took only $10.1 \pm 1.1$ s during PEMI.

Similarly, the rise in MAP to 50% of its maximum change from the nadir took $37.6 \pm 6.5$ s in the control condition but only $15.0 \pm 2.4$ s during PEMI.

Figure 6 shows the slopes of the rapid rises in HR, SV, and CO during the first 5 s after thigh-cuff release. The slopes for HR and SV did not significantly differ between the two conditions, whereas the slope for CO was steeper during PEMI than control.

We reached same conclusion when we calculated the AUC, the recovery slopes for MAP and TVC and the response slopes for HR, SV, and CO using the hemodynamic data expressed as
percentages of the respective baseline values. For that reason, only the results using the absolute values are presented.

DISCUSSION

To the best of our knowledge, this is the first study examining the effects of the muscle metaboreflex on dynamic cardiovascular responses to acute systemic hypotension in humans. The major finding of this investigation is that the arterial baroreflex-mediated recovery of MAP from thigh-cuff release-induced hypotension is significantly faster when it occurs while the muscle metaboreflex is activated. The faster recovery of MAP during PEMI was accomplished through rapid vasoconstriction following thigh-cuff release-induced transient vasodilation. To confirm this observation, we evaluated the hemodynamic variables using three independent approaches, Finometer measurements, Doppler ultrasound, and electrocardiography, which all revealed faster recovery during PEMI. These results show that arterial baroreflex-mediated peripheral vasoconstriction elicited in humans in response to acute systemic hypotension is augmented by the activation of the muscle metaboreflex, which results in a faster recovery of MAP. Our observations document the functional importance of the interaction between the arterial baroreflex and the muscle metaboreflex for blood pressure regulation in the context of acute systemic hypotension.

Thigh-cuff release after suprasystolic resting ischemia is a classic technique for inducing acute systemic hypotension without the use of drugs or changes in the concentration of vasoactive substances in the blood (1, 31). Arterial blood pressure was abruptly reduced by thigh-cuff release and remained low for a period of several seconds, after which arterial baroreflex-mediated cardiovascular effects gradually restored blood pressure toward baseline. In the present study, we found that dynamic cardiovascular responses induced by thigh-cuff
release were altered by activation of the muscle metaboreflex. Calculation of the AUCs revealed that all of the measured hemodynamic parameters except SV returned toward baseline faster during PEMI than in the control condition. The faster recovery in arterial blood pressure was caused by strong rapidly developing peripheral vasoconstriction. Given the more rapid arterial blood pressure recovery seen during PEMI, arterial baroreflexes would be expected to reload more quickly, which is consistent with our observation that baroreflex-mediated rises in HR and CO decayed within a shorter period. In addition to the shorter period of baroreflex unloading, the period over which left ventricular afterload declined was also shorter. This could be the main reason why SV tended to return toward baseline faster during PEMI and could have also contributed to the faster return in CO.

We previously showed that when the muscle metaboreflex is activated, unloading the carotid baroreflex by applying neck pressure evokes greater increases in MSNA, peripheral vasoconstriction, and arterial blood pressure than occurs under control conditions (13, 19). In addition, we and others have shown that the sensitivity of the arterial baroreflex control over MSNA is enhanced when the muscle metaboreflex is activated (7, 16–18, 24). The results of the present study are in good accord with those earlier findings and provide further evidence that arterial baroreflex-mediated sympathetic vasoconstriction is augmented when the muscle metaboreflex is activated. Moreover, our results reveal that vasoconstriction speeds are enhanced during the recovery of arterial blood pressure following evoked systemic hypotension such that MAP recovers within less than half the time it takes under control conditions. It is clear that during muscle metaboreflex activation, the arterial baroreflex is reset to function around higher blood pressures. In addition, it also appears that with respect to baroreflex gain as it relates to sympathetic vascular control, at least one portion of the stimulus-response relationship, i.e., the response to baroreceptor unloading, is enhanced during muscle metaboreflex activation (7, 13, 16–19, 24, 34). This modulation of baroreflex function would be advantageous for maintaining an elevated arterial blood pressure during activation of the muscle metaboreflex.

The 9-min arterial occlusion used in the present study likely provides a highly potent metabolic vasodilatory stimulus to the vasculature of the lower limbs (40, 41), and the rapid increase in TVC after thigh-cuff release would reflect the strong vasodilation in the lower limbs. Furthermore, myogenic vasodilation may also be evoked by the sharp fall in arterial blood pressure and contribute to the increase in TVC. The reduction in the maximum rise in TVC seen during PEMI is consistent with earlier reports showing that maximal metabolic vasodilation is counteracted by increases in sympathetic tone (27, 40). In addition, arterial baroreflex-mediated sympathetic vasoconstriction may have begun to work within only 5 to 8 s after the start of the fall in arterial blood pressure (13, 32), and the rise in arterial blood pressure from its nadir could have induced a myogenic stimulus for vasoconstriction. Therefore, the time course of the TVC responses would be derived from multiple simultaneously active factors affecting vascular regulation. Notably, the vasculature within human skeletal muscles is capable of robust vasodilation; indeed the peripheral blood flow capacity exceeds the maximal CO (2, 3). During systemic maximal exercise, therefore, some regulatory system must be interposed between the heart and the periphery to maintain homeostasis. It has been postulated that the sympathetic nervous system serves to control peripheral vascular conductance and acts to prevent cardiac function from being outstripped by peripheral metabolic needs (3, 4, 42); on the one hand, the accumulation of metabolites in exercising muscles causes vasodilation; on the other hand, the metabolites trigger the muscle metaboreflex, thereby increasing sympathetic nerve activity. In that context, the muscle metaboreflex may play a pivotal role as a counterbalance to metabolic vasodilation (8, 14, 20, 22, 23). In addition to the direct influence of the muscle metaboreflex on sympathetic activation, this reflex also affects cardiovascular regulation by modulating arterial baroreflex function (7, 13, 15–19, 24, 34). Enhanced arterial baroreflex-mediated vasoconstriction occurring when metabolites accumulate in the muscles, i.e., during activation of the muscle metaboreflex, ought to be an excellent defense against systemic hypotension induced by metabolic vasodilation. Interaction between the arterial baroreflex and muscle metaboreflex would thus provide an important functional link between metabolism within active muscles and blood pressure control, which would contribute to cardiovascular regulation during exercise.

In contrast to the important augmentation of baroreflex-mediated peripheral vasoconstriction, we did not find significant changes in the rapid baroreflex-mediated rise in HR in response to hypotension during PEMI. This finding is consistent with earlier reports showing that the HR response to neck pressure is not altered during PEMI (13, 19, 34). The rapid HR response to hypotension would be predominantly mediated via baroreflex control of cardiac parasympathetic activity (9), and our results suggest that activation of the muscle metaboreflex has little impact on that response. Nishiyasu et al. (29) showed that cardiac parasympathetic tone increases during PEMI in humans. They suggested that such an increase might form part of a counteraction by the arterial baroreflex in response to the rise in blood pressure induced by the muscle metaboreflex. Interestingly, Watanabe et al. (43) recently reported that the magnitudes of the changes in the sensitivity of baroreflex control of HR during PEMI varies considerably among individuals and that these changes in baroreflex sensitivity correlate positively with changes in cardiac parasympathetic tone. Consistent with those findings, we observed a great deal of variation in the change in the rapid HR response between the arterial baroreflex and muscle metaboreflex on sympathetic activation, this reflex also affects cardiovascular regulation by modulating arterial baroreflex activity. In that context, the muscle metaboreflex may play a pivotal role as a counterbalance to metabolic vasodilation (8, 14, 20, 22, 23). In addition to the direct influence of the muscle metaboreflex on sympathetic activation, this reflex also affects cardiovascular regulation by modulating arterial baroreflex function (7, 13, 15–19, 24, 34). Enhanced arterial baroreflex-mediated vasoconstriction occurring when metabolites accumulate in the muscles, i.e., during activation of the muscle metaboreflex, ought to be an excellent defense against systemic hypotension induced by metabolic vasodilation. Interaction between the arterial baroreflex and muscle metaboreflex would thus provide an important functional link between metabolism within active muscles and blood pressure control, which would contribute to cardiovascular regulation during exercise.

The rapid rise in SV immediately after the thigh-cuff release could have been the result of an abrupt decrease in afterload and/or sudden increase in preload because of a sharp rise in venous return. The initial SV response tended to be greater during PEMI than control (P = 0.11), and the initial reduction in MAP (i.e., afterload) was 5 mmHg greater during PEMI.
than control, which may have contributed to the slightly higher SV response. In addition, left ventricular contractility may have been performed via activation of the muscle metaboreflex (6, 29, 37), which would have also augmented the initial SV response. Importantly, the initial CO response was significantly increased during PEMI. The increased CO response should reflect increases in the HR response and/or SV response. Therefore, although we observed no apparent augmentation of either the baroreflex HR response or the initial SV response, the CO response, which reflects both baroreflex and intrinsic myocardial regulation, was enhanced and may have contributed to a buffering of the abrupt decrease in arterial blood pressure during PEMI.

Methodological considerations. In the present study, subjects performed the isometric handgrip exercise only during the PEMI trial (i.e., protocol 2). Isometric handgrip exercise is known to augment both cardiovascular and respiratory responses. The evoked enhancement of respiratory responses (e.g., hyperventilation) could affect sympathetic vasoconstiction and several dependent variables in this study. However, it has been demonstrated that respiratory volume (i.e., minute ventilation) as well as gas-exchange parameters (oxygen uptake and carbon dioxide production) return to resting levels within first minute after cessation of the isometric handgrip exercise during PEMI (21). It is therefore unlikely that the observed differences in cardiovascular responses between the control and PEMI trials are importantly influenced by changes in respiration evoked during handgrip exercise.

The intervention employed to induce acute systemic hypotension in this study creates reactive hyperemia in the lower limbs. It has been reported that the extent of the reactive hyperemia is reduced under conditions of increased sympathetic tone (5, 11, 12). Given that sympathetic tone increased during PEMI, the smaller increase and faster recovery of TVC might be due in part to the attenuated reactive hyperemia. This additional mechanism, which likely functions independently of baroreflex modulation, may have contributed to the faster recovery in blood pressure observed during PEMI.

In conclusion, the results obtained in this study show that when the muscle metaboreflex is activated in humans, peripheral vasoconstriction mediated by the arterial baroreflex in response to acute systemic hypotension is augmented, which speeds the recovery of MAP. Our observations demonstrate the functional importance of the interaction between the arterial baroreflex and the muscle metaboreflex for blood pressure regulation in the context of acute systemic hypotension. We suggest that such modulation of baroreflex function is one of the mechanisms by which elevation of arterial blood pressure is maintained during activation of the muscle metaboreflex.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

M.I., N.K., and T.N. conception and design of research; M.I., K.W., and N.f. performed experiments; M.I. analyzed data; M.I. and T.N. interpreted results of experiments; M.I. prepared figures; M.I. and T.N. drafted manuscript; M.I. and T.N. edited and revised manuscript; M.I., K.W., N.f., N.K., and T.N. approved final version of manuscript.

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