Time-dependent modulation of arterial baroreflex control of muscle sympathetic nerve activity during isometric exercise in humans

Masashi Ichinose, Mitsuru Saito, Narihiko Kondo, and Takeshi Nishiyasu. Time-dependent modulation of arterial baroreflex control of muscle sympathetic nerve activity during isometric exercise in humans. Am J Physiol Heart Circ Physiol 290: H1419–H1426, 2006. First published November 11, 2005; doi:10.1152/ajpheart.00847.2005.—We investigated the time-dependent modulation of arterial baroreflex (ABR) control of muscle sympathetic nerve activity (MSNA) that occurs during isometric handgrip exercise (IHG). Thirteen healthy subjects performed a 3-min IHG at 30% maximal voluntary contraction, which was followed by a period of imposed postexercise muscle ischemia (PEMI). The ABR control of MSNA (burst incidence and strength) was followed by a period of imposed postexercise muscle ischemia (PEMI). The ABR control of MSNA (overall MSNA control) was increased at IHG2. During PEMI, the ABR control of total MSNA was the same as at IHG2. During PEMI, the ABR control of muscle sympathetic nerve activity was modulated in a time-dependent manner. We suggest that this modulation of ABR function is one of the mechanisms underlying the progressive increase in blood pressure and MSNA during the course of isometric exercise.

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METHODS

Subjects. We studied 13 healthy volunteers (10 men and 3 women) with a mean age of 23 ± 1 yr, a body weight of 62.4 ± 3.1 kg, and a height of 170.1 ± 0.3 cm. None of the subjects was receiving medication, and none smoked. The study, which was carried out 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.

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, from which we determined the MVC. Scherrer et al. (44) showed that ABRs more effectively buffer reflex increases in muscle SNA (MSNA) during isometric handgrip exercise (IHG) than under resting conditions. Moreover, Kamiya et al. (18) reported that ABRs are reset to function at higher arterial pressures, and the sensitivity of their control of MSNA is elevated during both IHG and postexercise muscle ischemia (PEMI). These findings suggest that ABR control of MSNA is modulated during isometric exercise and that time-dependent alterations in ABR function are a key determinant of the MSNA responses during isometric exercise. Consistent with that idea, both the number of MSNA bursts (burst frequency and/or burst incidence) and the MSNA burst strength (amplitude or area of bursts) progressively increase during isometric exercise (42, 43, 46, 47, 51, 52), and both are influenced by ABRs on a beat-to-beat basis (4, 8, 19, 48, 53, 54). Moreover, we recently found that the modulation of the ABR control of MSNA (overall MSNA control) seen during PEMI could be a consequence of altered ABR control of both the occurrence and strength of MSNA bursts (15). Whether and how the ABR-mediated control of the occurrence and strength of MSNA bursts is modulated during isometric exercise have never been examined in humans, however. The purpose of the present study, therefore, was to test our working hypotheses that, in humans, ABR-mediated beat-to-beat controls of the occurrence and strength of MSNA bursts and overall MSNA are all modulated in a time-dependent manner during the course of IHG.
experiment. Auditory signals and an oscilloscope display of respiratory volume were supplied to assist the subject in this. The purpose of the controlled breathing was to avoid breath holding and Valsalva maneuvers and to keep the effect of breathing on MSNA constant throughout the experiment. Control data were acquired for 4 min before the start of handgrip exercise, after which the subject performed a 3-min IHG at 30% MVC with visual feedback of the achieved force through an oscilloscope display. Five seconds before the cessation of the IHG, the occlusion cuff was inflated to supersystolic pressure (>240 mmHg) and remained inflated long enough to produce a 4-min period of PEMI. After PEMI, the cuff was deflated. From the 5-min recording made during the recovery period, we used the 4-min-long record starting at 1 min after cuff deflation for analysis.

Measurements. HR was monitored via a three-lead electrocardiogram (ECG). 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 the level of the heart. The subject wore a mask connected to a respiratory flowmeter (RF-H; Minato Medical Science) for measurement of respiratory flow and tidal volume. The analog signals representing the ECG, blood pressure waveforms, respiratory flow, respiratory volume, and mean voltage neurogram (see below) were continuously recorded on an FM magnetic tape data recorder (MR-30; TEAC). The data were also digitized at a sampling frequency of 400 Hz through an analog-to-digital converter (Maclab/8e; AD Instruments) and fed into a personal computer (Powerbook 1400C; Apple). In addition, individual ratings of perceived exertion (RPE; based on the Borg scale of 6 to 20) were obtained at the end of each minute of IHG (2).

Multiunit muscle sympathetic nerve discharge was recorded using the microneurographic technique. A tungsten microelectrode with a shaft diameter of 0.1 mm and an impedance of 1–5 MΩ was inserted manually by an experimenter into the tibial nerve at the popliteal fossa and then adjusted until MSNA was recorded. The criteria to identify MSNA were spontaneous burst discharges synchronized with the heart beat and enhanced by Valsalva maneuvers or apnea but unaffected by cutaneous touch or arousal stimuli (4, 43, 50). The experimenter did not touch the intraneural electrode once the experimental protocol had begun. The neurogram was fed to a differential amplifier, amplified 100,000 times through a band-pass filter (500–3,000 Hz), and then full-wave rectified and integrated using a capacitance-integrated circuit with a time constant of 0.1 s. The mean voltage neurogram was continuously recorded on FM tape and digitized as described above.

Data analysis. Beat-to-beat heart rate was calculated from the R-R intervals on the ECG. Beat-to-beat systolic and diastolic arterial pressures (SAP and DAP, respectively) were obtained from the arterial pressure waveform. Mean arterial pressure (MAP) was calculated using the equation MAP = DAP + (SAP − DAP)/3.

During the 4-min control period, MSNA bursts were identified by inspection of the mean voltage neurogram while the subject maintained constant breathing. The voltage levels during the periods between bursts were then averaged, and this level was taken as zero. The largest burst occurring during this rest period was assigned a value of 1,000, and MSNA data were normalized with respect to this standard in each subject. The amount of SNA under each condition was expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats). Burst strength, obtained from the mean area of the MSNA bursts recorded under each condition, was expressed as mean burst strength (arbitrary units). Total MSNA was taken as the product of the mean burst strength and burst frequency. The hemodynamic and MSNA variables were averaged over the 4-min control period, over each minute of the IHG, and over the 4-min PEMI and recovery periods, respectively.

The assessment of ABR modulation of burst incidence, burst strength, and total MSNA has been described in detail elsewhere (15). Briefly, the relationships between SAP and burst incidence, burst strength, and total MSNA during the control period, at each minute of IHG, and during the PEMI and recovery periods were analyzed as follows. 1) Taking into account the latency from the R wave of the ECG to the sympathetic burst (7), we related the DAP for each individual heart beat to the corresponding MSNA data. Because changes in MSNA correlate closely with changes in SAP, but not with changes in SAP (48), we used DAP in this analysis. 2) All DAP values measured under each condition were grouped into 1-mmHg bins. In each group, diastoles were inspected to see whether they were associated with an MSNA burst, and we then calculated the percentage of diastoles associated with an MSNA burst (burst incidence per beat). 3) We used the signal-averaging technique to determine the burst strength and total MSNA for each diastolic-pressure bin (13). The MSNA signals were averaged over a period corresponding to the length of the heartbeat by taking into account the presumed latency from the R wave of the ECG, after which the area under the averaged MSNA signal was calculated. To calculate the burst strength related to each DAP bin (burst strength per beat), only those MSNA signals associated with a burst were selected, and these were averaged to allow us to calculate the area of the averaged MSNA signal using the above-mentioned technique. The total activity related to each DAP bin (total MSNA per beat) was calculated as the area of the averaged MSNA signal created from all the MSNA signals in each bin, whether or not they were associated with an MSNA burst. 4) The calculated burst incidence, burst strength, and total activity obtained for each DAP bin were plotted against the corresponding DAP, after which linear regression analysis was carried out for each diagram. Because the relationship between MSNA and DAP was often nonlinear at high blood pressures due to complete inhibition of MSNA, regression lines were constructed by using only the linear part of the data. We took the slope of each line as indicating sensitivity of the ABR control of each variable. The points corresponding to the average DAP on the regres-
Arterial baroreflex control of MSNA during exercise

Table 1. Arterial blood pressure, HR, and MSNA during the control period, each minute of IHG, and the PEMI and recovery periods

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>IHG1</th>
<th>IHG2</th>
<th>IHG3</th>
<th>PEMI</th>
<th>Recovery</th>
</tr>
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<tbody>
<tr>
<td>SAP, mmHg</td>
<td>126±3.3†</td>
<td>136±2.8†</td>
<td>147±3.0†</td>
<td>161±3.1†</td>
<td>159±2.5†</td>
<td>135±2.5†</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>67±2.0†</td>
<td>72±2.1†</td>
<td>81±2.0†</td>
<td>92±2.2†</td>
<td>86±2.8†</td>
<td>69±2.0†</td>
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<tr>
<td>MAP, mmHg</td>
<td>87±2.0†</td>
<td>93±1.6†</td>
<td>103±1.7†</td>
<td>115±1.8†</td>
<td>110±2.1†</td>
<td>90±1.6†</td>
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<tr>
<td>PP, mmHg</td>
<td>59±3.3†</td>
<td>64±3.7†</td>
<td>66±3.7†</td>
<td>70±3.8*</td>
<td>72±3.4*</td>
<td>66±3.2†</td>
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<tr>
<td>HR, beats/min</td>
<td>63±3.6</td>
<td>72±3.6†</td>
<td>75±3.9†</td>
<td>81±4.5†</td>
<td>66±3.2</td>
<td>63±2.5</td>
</tr>
<tr>
<td>MSNA burst frequency, bursts/min</td>
<td>14.6±1.6†</td>
<td>17.8±1.9†</td>
<td>26.8±3.1*</td>
<td>36.7±2.9*</td>
<td>29.7±2.3*</td>
<td>15.4±1.7†</td>
</tr>
<tr>
<td>MSNA burst incidence, bursts/100 heartbeats</td>
<td>23.1±2.0†</td>
<td>25.0±2.4†</td>
<td>35.8±3.6†</td>
<td>45.0±2.5*</td>
<td>45.4±3.3*</td>
<td>24.7±2.6†</td>
</tr>
<tr>
<td>Mean burst strength, AU</td>
<td>103.0±6.1†</td>
<td>119.3±7.4†</td>
<td>159.2±12.1*</td>
<td>191.6±17.0†</td>
<td>157.4±10.4*</td>
<td>111.7±10.6†</td>
</tr>
<tr>
<td>Total activity (mean burst strength × burst frequency)</td>
<td>1.527±196†</td>
<td>2.215±313†</td>
<td>4.169±537*</td>
<td>6.769±567†</td>
<td>4.638±464*</td>
<td>1.814±294†</td>
</tr>
<tr>
<td>RPE</td>
<td>14.2±0.4</td>
<td>16.6±0.4</td>
<td>19.0±0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. PEMI, postexercise muscle ischemia; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; RPE, ratings of perceived exertion; IHG, isometric handgrip exercise; IHG1, IHG2, and IHG3 are first, second, and third minute of IHG. *Significant difference from control, P < 0.05. †Significant difference from PEMI, P < 0.05.

RESULTS

Basal data. Table 1 shows the changes in arterial blood pressure, HR, and MSNA that occurred during the control period, at each minute during IHG, and during the PEMI and recovery periods. During IHG, the values of SAP, DAP, MAP, pulse pressure (PP), and HR increased progressively. During the subsequent PEMI, the values for SAP, DAP, MAP, and PP were all higher than during the control period, but HR was not different; DAP and MAP were lower than at the third minute of IHG (IHG3), but higher than at the second minute of IHG (IHG2). At the first minute of IHG (IHG1), there was no significant change from control in any of the MSNA variables. At IHG2, all of the MSNA variables were significantly ele-

Fig. 2. Linear relationships between MSNA burst incidence and diastolic blood pressure (DAP) during the control period (A–D, open circles, dashed lines); at the 1st minute of IHG (IHG1; A, filled circles, solid line), IHG2 (B, filled circles, solid line), and IHG3 (C, filled circles, solid line); and during the PEMI (A–D, open triangles, dashed line) and recovery (D, filled circles, solid line) periods in a representative subject. The larger symbols show the prevailing points (PPo) at the indicated times during the experimental protocol.
vated from control and were increased further at IHG3. During PEMI, all of the MSNA variables remained above control; burst frequency, mean burst strength, and total MSNA were all lower than that at IHG3, whereas burst incidence was comparable to IHG3. During recovery, SAP and PP were still higher than control, whereas DAP, MAP, and HR had returned to control levels. All MSNA variables returned to control levels during the course of the recovery period. RPE gradually increased during IHG, nearly reaching the fatigue level by IHG3.

**ABR control of MSNA burst incidence.** The linear regression analyses relating burst incidence to DAP for a representative subject are shown in Fig. 2; the group mean prevailing point and the regression lines at each of the indicated times are shown in Fig. 3. The derived variables describing the ABR control of burst incidence are presented for the group in Table 2. All subjects showed significant negative correlations between burst incidence and DAP during the control period, at each minute of IHG, and during the PEMI and recovery periods. During IHG, the linear relationship between burst incidence and DAP was progressively shifted rightward, indicating a time-dependent resetting of ABR operating pressure to higher blood pressures. Then at IHG2, the prevailing point was also significantly shifted upward and was shifted further upward at IHG3. During PEMI, the relationship was shifted back to a blood pressure lower than that at IHG3 but slightly higher than that at IHG2, although the prevailing point remained at the same level as at IHG3. The relationship between burst incidence and DAP and the prevailing point returned to control levels during the recovery period. The slope of the linear regression line relating burst incidence and DAP (sensitivity of ABR control of burst incidence) remained unchanged throughout the experiment.

**ABR control of MSNA burst strength.** The relation between DAP and burst strength was similar to that between DAP and burst incidence (Fig. 4). During IHG, the linear regression line relating burst strength and DAP gradually shifted rightward. Then at IHG2, it was shifted upward and was shifted further upward at IHG3, as evidenced by the significant increases in mean burst strength (Table 1). During PEMI, the relationship was reset back to blood pressures slightly higher than at IHG2 and was also shifted downward from the IHG3 to the IHG2 level. The relationship between burst strength and DAP returned to control levels during the recovery period. As with burst incidence, the slope of the linear regression line was not significantly changed during the experiment.

**ABR control of total MSNA.** The linear regression analyses relating total MSNA and DAP for a representative subject are shown in Fig. 5; the group mean prevailing point and regression lines at the indicated times are shown in Fig. 6. The derived variables describing the ABR control of total MSNA are presented for the group in Table 3. All subjects exhibited significant negative correlations between total MSNA and DAP at all of the times examined. As with burst incidence and strength, the relationship between total MSNA and DAP shifted progressively rightward during IHG, and the prevailing point was significantly shifted upward at IHG2 and shifted further upward at IHG3. In contrast to burst incidence and strength, however, the slope of the regression line relating DAP to total MSNA became more negative at IHG2 and far more negative at IHG3, indicating increased sensitivity of ABR control of total MSNA. A partial reversal was seen during PEMI. The relation was shifted back to a blood pressure lower than that at IHG3 but slightly higher than at IHG2. The prevailing point was shifted downward from the IHG3 to the IHG2 level, and the slope of the regression line became less negative than at IHG3 and was comparable to that seen at IHG2. The linear relationship between total MSNA and DAP, prevailing point, and those slopes all returned to control levels during the recovery period.

**DISCUSSION**

The major finding of this investigation is that the ABR control over burst incidence, burst strength, and total MSNA was time dependently modulated during the course of IHG. At IHG1, the linear relationship between DAP and each of the MSNA variables (DAP-MSNA lines) was shifted rightward without significant vertical shift or change in sensitivity of ABR control of MSNA (slope). However, at IHG2, the DAP-MSNA lines were shifted both rightward and upward, and the sensitivity of the ABR control of total MSNA was increased. At IHG3, the DAP-MSNA lines were shifted further rightward and upward, and the sensitivity of the ABR control of total MSNA was increased beyond that at IHG2. Thus the ABR control of MSNA was not uniform throughout the course of IHG.

Table 2. Derived variables describing the arterial baroreflex control of burst incidence

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>IHG1</th>
<th>IHG2</th>
<th>IHG3</th>
<th>PEMI</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope of incidence line, bursts/100 heartbeats/100 mmHg^-1</td>
<td>-5.00±0.40</td>
<td>-6.45±0.86</td>
<td>-4.85±0.51</td>
<td>-5.67±0.33</td>
<td>-5.66±0.51</td>
<td>-4.45±0.39</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>-0.88±0.02</td>
<td>-0.78±0.03</td>
<td>-0.71±0.02</td>
<td>-0.75±0.02</td>
<td>-0.86±0.02</td>
<td>-0.85±0.02</td>
</tr>
<tr>
<td>Prevailing point, bursts/100 heartbeats</td>
<td>21.0±1.55†</td>
<td>21.1±2.37†</td>
<td>31.8±3.69*†</td>
<td>41.3±2.56*</td>
<td>40.2±3.03*</td>
<td>20.6±2.77†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Prevailing point, point on the regression line corresponding to mean diastolic blood pressure. *Significant difference from control, P < 0.05. †Significant difference from PEMI, P < 0.05.
Fig. 4. Linear relationships between MSNA burst strength and DAP during the control period (A–D, open circles, dashed line); at IHG1 (A, filled circles, solid line), IHG2 (B, filled circles, solid line), and IHG3 (C, filled circles, solid line), and during the PEMI (A–D, open triangles, dashed line) and recovery (D, filled circles, solid line) periods in a representative subject.

Fig. 5. Linear relationships between total MSNA and DAP in a representative subject. The symbols are the same as in Fig. 2.
It has been suggested that at the onset of exercise, ABR operating pressures are rapidly reset to a higher level (5, 39, 40). The rapid increase in HR and simultaneous increase in blood pressure seen at the onset of both isometric and dynamic exercise (5, 24, 25), and this, too, is thought to be caused by the rapid resetting of ABR (5, 39, 40). In humans, however, MSNA does not significantly increase until ~60 s after the onset of IHG (at ~30% MVC) (42, 44, 46, 47, 51, 52). Although the mechanism(s) of the difference in the response of renal SNA to the onset of exercise in animals and the response of MSNA in humans is unclear, it could be attributable to species differences (e.g., a difference in adaptation levels to aerobic metabolism) and/or differential regulation of renal SNA and MSNA by exercise (see Limitations for more details on this issue). Interestingly, Scherrer et al. (44) showed that within the first minute of IHG (33% MVC), MSNA was increased in subjects receiving nitroprusside to suppress the IHG-induced rise in blood pressure; conversely, MSNA was suppressed in subjects receiving phenylephrine to accentuate the IHG-induced elevation in blood pressure. Those results suggest that the lack of change in MSNA from the resting level at IHG1 is due, at least in part, to ABR control of MSNA. Our finding that the DAP-MSNA relations were shifted rightward (ABR resetting) without a significant vertical shift or change in sensitivity of ABR control of MSNA suggests that, at IHG1, the ABR operating pressures are reset, enabling MSNA to be maintained at the resting level despite an increase in blood pressure.

Rowell and O’Leary (39) hypothesized that two neural inputs, central command and feedback originating within the working muscles, are involved in the resetting of ABR control of SNA during exercise. They postulated that central command resets the ABR operating point to a higher pressure (rightward shift), while the muscle reflex-induced increase in SNA causes a vertical shift in the ABR function curve (relation between blood pressure and SNA). When combined, these two mechanisms would result in parallel upward and rightward resetting such as that seen in the present study. Furthermore, our observation that RPE was 14.2 ± 0.4 at IHG1 suggests that central command was mildly activated at that time, although the muscle metaboreflex would not be, which is consistent with DAP-MSNA relations being shifted only rightward. On the other hand, recent studies investigating the carotid baroreflex control of HR and MAP suggest that central command causes both lateral and vertical shifts in the carotid baroreflex-HR function curve and carotid baroreflex-MAP function curve in humans (10, 33). The difference between those results and ours is likely related to the fact that we investigated ABR control of MSNA, which involves both carotid and aortic baroreflexes. It may be that the effects of central command on ABR control of MSNA differ from its effects on the carotid baroreflex control of MSNA and/or its effects on ABR control of HR and MAP.

Although there is currently no direct evidence, the muscle mechanoreflex is also thought to contribute to the cardiovascular responses at the onset of isometric exercise (29, 39, 40), inducing ABR resetting during isometric exercise in animals (27, 36) and during dynamic exercise in humans (17). Its effect on ABR function during isometric exercise in humans is still unknown, however. The results of the present study suggest that if the muscle mechanoreflex is activated at IHG1 and exerts some effect on ABR function, it may act to reset the ABR operating pressures, but it would not cause a vertical shift of the DAP-MSNA lines or a change in the sensitivity of ABR control of MSNA.

Our findings suggest that activation of the muscle metaboreflex could account for both an upward and rightward shift in the DAP-MSNA relations as well as the increase in the sensitivity of ABR control of total MSNA. This idea is supported by the finding that the time-dependent modulation of the DAP-MSNA relations occurring during IHG persisted during PEMI, a time when the muscle metaboreflex would be activated in the absence of both central command and the muscle mechanoreflex (1, 15, 16, 30–32, 34, 39). The activation of the muscle metaboreflex would presumably be delayed from the onset of IHG by the gradual accumulation of metabolites in the vicinity of the metaboreceptor afferent endings (32, 37, 39, 40, 42, 43, 47, 51, 52), which would account for the almost 60-s latency from the onset of IHG to the onset of sympathetic activation (42, 44, 46, 47, 51, 52). For the same reason, the metaboreflex may not be sufficiently activated at IHG1 to mediate the upward shift in the DAP-MSNA relations and the increase in the sensitivity of ABR control of total MSNA. By IHG2 and PEMI, we believe, the metaboreflex would be sufficiently activated to account for both an upward and rightward shift in the DAP-MSNA relations as well as the increase in the sensitivity of ABR control of total MSNA.
IHG3, on the other hand, the metaboreflex would be sufficiently activated and involved to mediate the full response.

That the modulation of ABR control of MSNA observed at IHG3 (i.e., rightward and upward shift of DAP-MSNA lines and an increase in sensitivity) was greater than during PEMI indicates that mechanisms other than the muscle metaboreflex (i.e., central command and/or muscle mechanoreflex) are also involved in the modulation of ABR control of MSNA at IHG3. In that regard, our finding that RPE had nearly reached the fatigue level (RPE = 19.0 ± 0.3) at IHG3 indicates that central command should be severely activated by IHG3. According to Victor et al. (52), a mild to moderate level of central command has no effect on MSNA during IHG, whereas MSNA is increased when central command is severely activated. Thus, in addition to the resetting of the ABR operating pressure seen with even mild activation of central command (at IHG1), the severe activation of central command occurring at IHG3 could also account for the upward shift of DAP-MSNA relations and the increase in the sensitivity of ABR control of total MSNA.

During PEMI, the DAP-burst strength and DAP-total activity relations were shifted leftward and downward from those at IHG3 (i.e., back toward control levels). By contrast, the DAP-burst incidence relation was only shifted leftward. That the upward shift in the DAP-burst incidence relation was sustained from IHG3 to PEMI indicates it is mediated mainly by the muscle metaboreflex. In addition, it appears that whereas central command and/or the muscle mechanoreflex may shift the DAP-burst strength and DAP-total MSNA relations both vertically and laterally, they shift the DAP-burst incidence relation only laterally. This suggests that modulation of ABR control of burst occurrence and burst strength by the muscle metaboreflex differs from that by central command and/or muscle mechanoreflex. Although evidence of differential control of the occurrence and strength of sympathetic bursts has been obtained both in animals (20–22) and in humans (14, 15, 19, 49), the mechanism remains unknown (26).

Limitations. There are several limitations to our approach to evaluating ABR control of MSNA on the basis of spontaneous fluctuations in DAP and MSNA. Although a linear relationship between MSNA and DAP has been demonstrated in previous studies (18, 19, 48), spontaneous blood pressure fluctuations are not particularly large, so the ABR stimulus-response range that can be examined using this method is narrow (within 20 mmHg). Although this is a narrower range than is obtained using the neck-chamber technique (6, 16, 53) or invasive pharmacological manipulation (3, 12), a 20-mmHg change in blood pressure is within the physiological range and should be a good reflection of the ABR control of MSNA under physiological conditions. Furthermore, to investigate the reflex effect elicited when two or more inputs are summed (e.g., ABR, muscle reflexes, and central command) it is important to use inputs that are small enough not to cause saturation of the output because of inherent limitations in the effector responses of the system (41). On that basis, our experimental results can be taken as revealing a physiological modulation of the ABR control of MSNA during IHG and PEMI. Moreover, the breathing frequency and tidal volume were fixed throughout the experiment (as far as possible), so the influence of changes in respiration on the modulation of the ABR control of MSNA would have been small.

We also need to consider the potential impact of fixed breathing on the stimulation of peripheral chemoreceptors. It is possible that the fixed breathing prevented the respiratory alkalemia that is reportedly induced by fatiguing isometric exercise (35), and, if so, the activity of peripheral chemoreceptors during IHG in the present study may be greater than during IHG without fixed ventilation. This increase in peripheral chemoreceptor activity may, in turn, enhance the MSNA response and possibly exert an effect on the ABR control of MSNA during IHG. Unfortunately, we measured no blood-gas or acid-base variables, so we can draw no definitive conclusions regarding this issue.

In the present investigation, we measured sympathetic nerve outflow to an inactive skeletal muscle bed and examined the ABR control of that activity during the course of IHG in humans. This does not preclude the possibility that the ABR control of sympathetic outflow and the resultant levels of SNA to other organs differ from the level of MSNA. Because it is known that the regulation of sympathetic outflow to various tissues can be highly differentiated [e.g., differential ABR regulation of renal, lumbar, and adrenal SNA has been demonstrated in rats (45)], our results on MSNA (i.e., levels of SNA and ABR control of SNA) cannot be generalized to SNA in other organs. A more complete understanding of the regulation of SNA mediated by ABR during isometric exercise in humans will require further investigation.

In conclusion, our results show that in human subjects, the ABR control of burst incidence, burst strength, and total MSNA was time dependently modulated during the course of IHG. We suggest that this modulation of ABR function is one of the mechanisms mediating the progressive increase in both blood pressure and MSNA in the course of isometric exercise.

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Present address of M. Ichinose: Faculty of Human Development, Kobe University, Kobe 657-8501, Japan.

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