Modulation of control of muscle sympathetic nerve activity during orthostatic stress in humans

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Ichinose, Masashi, Mitsuru Saito, Takeshi Ogawa, Keiji Hayashi, Narihiko Kondo, and Takeshi Nishiyasu. Modulation of control of muscle sympathetic nerve activity during orthostatic stress in humans. Am J Physiol Heart Circ Physiol 287: H2147–H2153, 2004; doi:10.1152/ajpheart.00215.2004.—We tested the hypothesis that orthostatic stress would modulate the arterial baroreflex (ABR)-mediated beat-by-beat control of muscle sympathetic nerve activity (MSNA) in humans. In 12 healthy subjects, ABR control of MSNA (burst incidence, burst strength, and total activity) was evaluated by analysis of the relation between beat-by-beat spontaneous variations in diastolic blood pressure (DAP) and MSNA during supine rest (CON) and at two levels of lower body negative pressure (LBNP: −15 and −35 mmHg). At −15 mmHg LBNP, the relation between burst incidence (bursts per 100 heartbeats) and DAP showed an upward shift from that observed during CON, but the further shift seen at −35 mmHg LBNP was only marginal. The relation between burst strength and DAP was shifted upward at −15 mmHg LBNP (vs. CON) and further shifted upward at −35 mmHg LBNP. At −15 mmHg LBNP, the relation between total activity and DAP was shifted upward from that observed during CON and further shifted upward at −35 mmHg LBNP. These results suggest that ABR control of MSNA is modulated during orthostatic stress and that the modulation is different between a mild (nonhypotensive) and a moderate (hypotensive) level of orthostatic stress.

arterial baroreflex; sympathetic nervous system; lower body negative pressure

The nature of the mechanisms controlling the cardiovascular system under orthostatic stress is an important research issue in physiology, especially in humans, who usually adopt an upright posture (27). The major cardiovascular responses to orthostatic stress are increases in peripheral vascular resistance and heart rate (HR), which are mediated by the autonomic nervous system (27). These adjustments are thought to be mediated by reflexes originating from the carotid sinus and aortic baroreceptors [arterial baroreflex (ABR)] and from stretch receptors in the cardiopulmonary region (cardiopulmonary baroreflex) (1, 4, 12, 20, 21, 23–25, 27, 30, 33, 36, 43). Periheral vascular resistance and muscle sympathetic nerve activity (MSNA) are progressively increased with an increasing severity of orthostatic stress (12, 14, 23, 28, 29, 33, 38, 40, 41). However, HR is not increased during mild, nonhypotensive orthostatic stress, although it is increased at moderate and high levels of orthostatic stress (sufficient to cause hypotension). It has therefore been assumed that these cardiovascular responses are dependent on the degree of unloading of the cardiopulmonary baroreflex and the ABR and on the balance between them (4, 12, 25, 28, 33, 36, 38, 43). However, the fundamental nature of the mechanisms underlying the beat-by-beat control of sympathetic vasomotor activity during a mild level of orthostatic stress (nonhypotensive orthostatic stress) and a moderate level of orthostatic stress (hypotensive orthostatic stress) remains unclear.

The number of MSNA bursts (burst frequency and/or burst incidence) and the MSNA burst strength (amplitude or area of bursts) are reportedly increased during orthostatic stress (at mild or moderate levels) (14, 29, 33, 38, 40). It has been demonstrated that the ABR influences the incidence and strength of MSNA bursts on a beat-by-beat basis, and this reflex is thought to be the major modulator of MSNA in humans (3, 6, 15, 16, 34, 41, 42). It has been hypothesized that ABR-mediated cardiovascular control is modulated by orthostatic stress (4, 25, 39). Indeed, some previous reports document the notion that carotid sinus baroreflex control of HR, blood pressure, and vascular resistance shows an increased sensitivity under orthostatic stress (25, 39). However, it is unknown whether and how ABR-mediated beat-by-beat control of the occurrence and strength of MSNA bursts, which can be investigated by examining the relation between MSNA and arterial blood pressure on a beat-by-beat basis (11), is modulated under orthostatic stress. Furthermore, the possibility that there might be a difference between mild and moderate orthostatic stress in ABR control of the occurrence and strength of such bursts has not been examined.

The purpose of this study was to investigate our working hypotheses that, in humans, ABR-mediated beat-by-beat control of the occurrence of MSNA bursts, strength of MSNA bursts, and overall MSNA is modulated during orthostatic stress and that this modulation of MSNA control may differ between mild and moderate orthostatic stress.

Methods

Subjects. We studied 12 healthy volunteers (11 men and 1 woman) with mean age of 25 ± 2 yr, body weight of 67.3 ± 1.8 kg, and height of 174.1 ± 1.2 cm. The subjects were nonsmokers, and none was taking any medication. 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 the supine position, with the lower torso to the iliac crest enclosed in the lower body negative pressure (LBNP) box. A small door at the bottom of the LBNP box allowed recording of MSNA (by microneurographic technique) from the tibial nerve at the popliteal fossa (31). After we had identified MSNA (see below for criteria), the door was closed and sealed for the LBNP protocol. After a 15-min rest period, data collection began.

Raw recordings obtained during supine rest (control), −15 mmHg LBNP, and −35 mmHg LBNP are shown in Fig. 1. The subject was instructed to maintain a constant rate of breathing (7.5 cycles/min) and a constant tidal volume of 0.7–1.0 liter (previously established as a tidal volume that did not cause dyspnea at a constant respiratory frequency of 7.5 cycles/min in each subject) throughout the experiment. Auditory signals and an oscilloscope display of respiratory volume were supplied to assist the subject maintain breathing rate and tidal volume as described above. Controlled breathing was used 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 5 min before application of LBNP. Then box pressure was decreased slowly to −15 mmHg (which required 20–28 s), kept constant for 5 min, and returned to the ambient pressure for 3 min. Thereafter, box pressure was decreased slowly to −35 mmHg (which required 45–60 s), kept constant for 5 min, and then returned to the ambient pressure.

**Measurements.** HR was monitored via a three-lead ECG. Beat-to-beat changes in blood pressure were assessed by finger photoplethysmography (Finapres 2300, Ohmeda), with the monitoring cuff placed around the middle finger and the forearm and hand supported so that the cuff was aligned at heart level. The subject wore a mask connected to a respiratory flowmeter (model RF-H, Minato Medical Science) for measurement of respiratory flow and tidal volume. LBNP box pressure was measured using a pressure transducer. The analog signals representing the ECG, blood pressure waveforms, respiratory flow, respiratory volume, box pressure, and mean voltage neurogram (see below) were continuously recorded on an FM magnetic-tape data recorder (model 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 then fed into a personal computer (Powerbook 1400C, Apple).

Multiunit muscle sympathetic nerve discharges were recorded by means of 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 to record MSNA. The criteria for MSNA were as follows: spontaneous burst discharges synchronized with the heartbeat and enhanced by Valsalva maneuver or apnea but showing no change in response to cutaneous touch or arousal stimuli (3, 31, 37). The experimenter did not touch the intraneural electrode after the 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 by a capacitance-integrated circuit with a time constant of 0.1 s. The mean voltage neurogram was continuously recorded on an FM magnetic-tape data recorder and also digitized with a sampling frequency of 400 Hz through an analog-to-digital converter for storage on a personal computer (see above).

**Data analysis.** Beat-by-beat HR was calculated from the R-R interval of the ECG. Beat-by-beat systolic and diastolic blood pressures were obtained from the arterial pressure waveform. Mean arterial pressure (MAP) was calculated as follows: MAP = DAP + (SAP − DAP)/3, where SAP and DAP are systolic and diastolic arterial blood pressures, respectively.

In a 5-min control period, during which the subject maintained constant breathing, MSNA bursts were identified by inspection of the mean voltage neurogram. Then the voltage levels in the periods between bursts were averaged, and this level was taken as zero. The largest burst occurring in 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 sympathetic nerve activity 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 in arbitrary units. Total MSNA was taken as the product of mean burst strength and burst frequency.

Assessment of ABR control of burst incidence, burst strength, and total MSNA using beat-by-beat spontaneous fluctuations in blood pressure and MSNA has been described in detail elsewhere (11). Briefly, we investigated ABR control of the three MSNA parameters during the control period and during application of −15 and −35 mmHg LBNP as follows. 1) Taking into account the latency from the R wave of the ECG to the sympathetic burst (5), we related the diastolic pressure of individual heartbeats to the corresponding MSNA data. Because changes in MSNA correlate closely with changes in DAP, but not with changes in SAP (34), we used DAP in this analysis. 2) All DAP values measured under each condition were grouped in 1-mmHg bins. In each group, diastoles were inspected to determine 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 (7). Briefly, we averaged the MSNA signals over a period corresponding to the length of the heartbeat, taking into account the presumed latency from the R wave of the ECG. Then we...

![Fig. 1. Raw data showing recorded variables during control, −15 mmHg lower body negative pressure (LBNP), and −35 mmHg LBNP in a representative subject. MSNA, muscle sympathetic nerve activity.](http://ajpheart.physiology.org/)
calculated the area under the averaged MSNA signal. To calculate the burst strength related to each diastolic pressure bin (burst strength per beat), only those MSNA signals associated with a burst were selected and averaged to allow us to calculate the area of the averaged MSNA signal using the above-mentioned technique. The total activity related to each diastolic pressure bin (total activity 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 diastolic pressure bin were plotted against the corresponding DAP, and linear regression analysis was performed for each diagram. The relation between MSNA and DAP was often nonlinear at high blood pressures, because MSNA was frequently completely inhibited at these pressures, so the regression line was constructed using only the linear part of the data. We took the slope of each regression line as indicating the ABR sensitivity for the control of each variable. The point corresponding to average diastolic pressure on the regression lines for burst incidence vs. DAP and total activity vs. DAP was taken as the prevailing point for a given relation.

Statistical analysis. Values are means ± SE. For physiological responses (arterial blood pressure, HR, and MSNA) and for the slope and prevailing point of the linear relation between MSNA and DAP, comparisons among control, −15 mmHg LBNP, and −35 mmHg LBNP were made using a one-way repeated-measures analysis of variance. Tukey’s post hoc test was used to assess group mean differences. In the analysis of the relation between burst incidence and DAP, the change in the prevailing point from control to −15 mmHg LBNP was compared with that from −15 to −35 mmHg LBNP using a paired t-test. The characteristics of the ABR relation between MSNA and DAP (DAP burst incidence, DAP burst strength, and DAP total activity) were determined by least-squares linear regression analysis. Statistical significance was accepted at P < 0.05.

RESULTS

Basal data. Table 1 shows the group values obtained for arterial blood pressure, HR, and MSNA during control, −15 mmHg LBNP, and −35 mmHg LBNP. At −15 mmHg LBNP, burst frequency, burst incidence, mean burst strength, and total MSNA were increased compared with control, although blood pressure and HR were not. Application of −35 mmHg LBNP caused further increases in burst frequency, mean burst strength, and total MSNA, but not burst incidence. At −35 mmHg LBNP, SAP and pulse pressure (PP) were decreased, whereas HR was increased (all vs. control). In addition, at −35 mmHg LBNP, PP was lower and HR was higher than at −15 mmHg LBNP.

ABR regulation of MSNA burst incidence. The linear regressions between burst incidence and DAP are shown in Fig. 2 for a representative subject; the derived variables describing 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 control, −15 mmHg LBNP, and −35 mmHg LBNP (r = −0.82 ± 0.04, −0.84 ± 0.03, and −0.86 ± 0.03, respectively; Table 2). At −15 mmHg LBNP, the linear relation and the prevailing point were shifted upward compared with control. At −35 mmHg LBNP, although the prevailing point tended to show a small increase from −15 mmHg LBNP, the change was not statistically significant. Indeed, the change in the prevailing point from −15 to −35 mmHg LBNP was significantly smaller than that from control to −15 mmHg LBNP (4.2 ± 2.16 vs. 9.0 ± 1.21 bursts/100 heartbeats, P < 0.05). Thus, at −35 mmHg LBNP, the upward shift, if any (vs. −15 mmHg LBNP), was significantly smaller than at −15 mmHg LBNP (vs. control). In 5 of 12 subjects, the prevailing point at −35 mmHg LBNP was

Table 1. Arterial blood pressure, HR, and MSNA during control, −15 mmHg LBNP, and −35 mmHg LBNP

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>−15 mmHg LBNP</th>
<th>−35 mmHg LBNP</th>
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<tbody>
<tr>
<td>SAP, mmHg</td>
<td>128±3.8</td>
<td>124±4.6</td>
<td></td>
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<tr>
<td>DAP, mmHg</td>
<td>72±2.8</td>
<td>72±2.8</td>
<td></td>
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<tr>
<td>MAP, mmHg</td>
<td>91±2.9</td>
<td>89±3.0</td>
<td></td>
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<tr>
<td>PP, mmHg</td>
<td>57±2.7</td>
<td>51±3.6</td>
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<tr>
<td>HR, beats/min</td>
<td>66±3.4</td>
<td>75±3.9†</td>
<td></td>
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<tr>
<td>MSNA burst frequency, bursts/min</td>
<td>19.6±2.2</td>
<td>25.9±2.2*</td>
<td></td>
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<tr>
<td>MSNA burst incidence, bursts/100 heartbeats</td>
<td>29.4±2.7</td>
<td>38.7±2.2*</td>
<td></td>
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<tr>
<td>Mean burst strength, AU</td>
<td>180±11.8</td>
<td>218±7.9†</td>
<td></td>
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<tr>
<td>Total activity</td>
<td>4,692±522*</td>
<td>6,900±389†</td>
<td></td>
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Table 2. Derived variables describing arterial baroreflex control of MSNA burst incidence

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>−15 mmHg LBNP</th>
<th>−35 mmHg LBNP</th>
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<tbody>
<tr>
<td>Slope of incidence line, bursts/100 heartbeats</td>
<td>−4.38±0.45</td>
<td>−4.57±0.44</td>
<td></td>
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<tr>
<td>Correlation coefficient</td>
<td>−0.82±0.04</td>
<td>−0.86±0.03</td>
<td></td>
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<tr>
<td>Prevailing point, bursts/100 heartbeats</td>
<td>26.3±3.22</td>
<td>35.3±2.33*</td>
<td></td>
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</table>

Values are means ± SE. Prevailing point, point on regression line corresponding to average DAP. *Significant difference from control, P < 0.05.
decreased, rather than increased, compared with −15 mmHg LBNP, whereas all subjects showed an increase in the prevailing point at −15 mmHg LBNP (vs. control). These results indicate that, at −35 mmHg LBNP, neither the linear relation nor the prevailing point showed a significant further shift upward from −15 mmHg LBNP. The slope of the relation did not differ among control, −15 mmHg LBNP, and −35 mmHg LBNP.

**ABR regulation of MSNA burst strength.** The linear regressions between burst strength and DAP are shown in Fig. 3 for a representative subject. Overall, the correlation coefficients during control, −15 mmHg LBNP, and −35 mmHg LBNP were −0.50 ± 0.08, −0.47 ± 0.12, and −0.58 ± 0.06, respectively. A significant negative correlation between burst strength and DAP was present for five subjects during control, six subjects at −15 mmHg LBNP, and eight subjects at −35 mmHg LBNP. The linear relation was shifted upward at −15 mmHg LBNP (vs. control) and further shifted upward at −35 mmHg LBNP (as also evidenced by the progressive increase in mean burst strength with increases in LBNP; Table 1). The slope of the linear regression line did not differ among control, −15 mmHg LBNP, and −35 mmHg LBNP (−6.39 ± 1.36, −6.55 ± 1.49, and −7.82 ± 1.22, respectively).

**ABR regulation of total MSNA.** The linear regressions between total MSNA and DAP are shown in Fig. 4 for a representative subject. The derived variables describing ABR regulation of total MSNA are presented for the group in Table 3. All subjects showed a significant negative correlation between burst incidence and DAP during control, −15 mmHg LBNP, and −35 mmHg LBNP ($r = -0.84 \pm 0.03$, $-0.82 \pm 0.03$, and $-0.86 \pm 0.03$, respectively; Table 3). At −15 mmHg LBNP, the linear relation and prevailing point were shifted upward from control and further shifted upward at −35 mmHg LBNP. The slope of the linear regression line did not differ among control, −15 mmHg LBNP, and −35 mmHg LBNP.

**DISCUSSION**

The major finding of this investigation was that, in human subjects, ABR controls of MSNA burst incidence, burst strength, and total activity were modulated under orthostatic stress. At a mild level of orthostatic stress, the relation between burst incidence and DAP was shifted upward from that obtained in control. However, at a moderate level of orthostatic stress, the relation between burst incidence and DAP was shifted upward from that obtained in control. In contrast, the relation between burst strength and DAP was progressively shifted upward with increasing severity of orthostatic stress. Consequently, the relation between total MSNA and DAP, which represents overall MSNA control, was progressively shifted upward with an increasing severity of orthostatic stress. These results suggest that in humans the modulation of ABR control of MSNA differs between mild and moderate orthostatic stress.

In the present study, we used −15 and −35 mmHg LBNP to simulate mild and moderate orthostatic stress, respectively. Although we did not measure central venous pressure (CVP), previous reports demonstrated that −15 mmHg LBNP is sufficient to decrease CVP (by ~3 mmHg) and to increase

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**Fig. 3.** Linear relation between MSNA burst strength and DAP during control, −15 mmHg LBNP, and −35 mmHg LBNP in a representative subject.

**Fig. 4.** Linear relation between total MSNA and DAP during control, −15 mmHg LBNP, and −35 mmHg LBNP in a representative subject.

**Table 3. Derived variables describing the arterial baroreflex control of total MSNA**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>−15 mmHg LBNP</th>
<th>−35 mmHg LBNP</th>
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<tr>
<td>Slope of total activity line, units/mmHg$^{-1}$</td>
<td>$-8.52 \pm 1.15$</td>
<td>$-9.96 \pm 1.36$</td>
<td>$-11.24 \pm 1.49$</td>
</tr>
<tr>
<td>Correlation coefficient, $r$</td>
<td>$-0.84 \pm 0.03$</td>
<td>$-0.82 \pm 0.03$</td>
<td>$-0.86 \pm 0.03$</td>
</tr>
<tr>
<td>Prevailing point, units/beat</td>
<td>38.1 ± 6.18</td>
<td>84.4 ± 16.50$^*$</td>
<td>125.8 ± 19.83$^*$†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Prevailing point, point on regression line corresponding to average DAP. *Significant difference from control, $P < 0.05$. †Significant difference from −15 mmHg LBNP, $P < 0.05$. 

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MSNA, whereas −35 mmHg LBNP causes a further reduction in CVP (by a further −3 mmHg) and an additional increase in MSNA (12, 14, 25, 27, 33, 38, 40, 43). These data are consistent with our results. Levels of LBNP that are insufficient to cause hypotension (less than −20 mmHg LBNP) have been presumed to unload cardiopulmonary baroreceptors but to have little or no effect on arterial baroreceptor afferent activity (12, 27, 43). However, according to Taylor et al. (36), the small reduction in central blood volume induced by a mild level of LBNP actually reduces the dimensions of the aortic baroreceptive areas. In the light of this finding, the modulations of the beat-by-beat control of MSNA mediated by ABR under mild and moderate levels of LBNP may be associated with unloading of the cardiopulmonary baroreflex and the ABR.

In humans, Sundlof and Wallin (34) quantified ABR control in terms of burst incidence and burst strength using the linear relation between spontaneous variations in DAP and muscle sympathetic nerve traffic. They also examined the relation between blood pressure and burst incidence during LBNP (−5 to −40 mmHg) (33) and reported that burst incidence correlated closely with DAP during LBNP, as it did in the control situation. However, a progressive modulation of ABR control of burst incidence at mild and moderate orthostatic stress has not been demonstrated. In agreement with their result, we found that the close relation between burst incidence and DAP was maintained across the situations examined (control and 2 levels of orthostatic stress; Table 2), suggesting that the dominance of ABR control of burst incidence is maintained under mild and moderate orthostatic stress as well as in the control situation. The slope of the linear relation between burst incidence and DAP, which represents the sensitivity of ABR control of burst incidence, was unaltered under mild and moderate orthostatic stress (vs. control; Fig. 2, Table 2). At a mild level of orthostatic stress, the relation between DAP and burst incidence was shifted upward, but there was no further significant shift during moderate orthostatic stress, despite a significant increase in MSNA from its level under mild orthostatic stress. These results suggest that orthostatic stress upwardly resets ABR control of burst incidence but that the magnitude of this upward resetting does not simply depend on the severity of the orthostatic stress.

In agreement with previous reports (14, 29, 33, 38, 40), burst frequency was progressively increased with increasing levels of LBNP (Table 1). Burke et al. (2) closely examined the quantitative aspects of the sympathetic nerve response to sitting and standing up from a supine position and found three patterns of increase in burst frequency. These were achieved via 1) an increased burst incidence, 2) an increased HR with a constant burst incidence, and 3) increases in burst incidence and HR. Although their results indicated an interaction between the control of HR and the control of burst incidence in the regulation of burst frequency, the underlying mechanisms remained uncertain. Our results show that during mild orthostatic stress the increase in burst frequency (vs. control) was accomplished by an upward resetting of ABR control of burst incidence without a change in HR. However, during moderate orthostatic stress, the increase in burst frequency (vs. mild orthostatic stress) was achieved without a significant alteration in ABR control of burst incidence but with an increase in HR. These results suggest that ABR controls of burst incidence and HR may interact to regulate burst frequency and that, especially during moderate orthostatic stress, the reflex increase in HR may not only maintain cardiac output but also help increase MSNA. However, other mechanisms could be invoked to explain the interrelation between the regulation of HR and the regulation of sympathetic activity. This area clearly needs further study.

In contrast to the results obtained for burst incidence, not all subjects showed a significant negative correlation between DAP and burst strength. Even in those in whom a significant correlation was present, the correlation coefficient was smaller than that obtained for burst incidence vs. DAP. The presence of a weak relation between DAP and burst strength suggests that the influence of the input from the arterial baroreceptors is not strong enough for ABR control of burst strength to be expressed to the same extent as the control of burst incidence. Possibly inputs other than those from arterial baroreceptors make a greater contribution to the control of burst strength. This notion is consistent with previous reports in animals (17–19) and in humans (9, 11, 15, 35). For example, arterial chemoreflex stimulation has been reported primarily to affect the amplitude of renal sympathetic nerve activity, rather than burst occurrence, in anesthetized cats (19). Moreover, an increase in MSNA burst amplitude (with an unchanged number of bursts) has been observed during mental stress in humans (9). In the present study, the relation between burst strength and DAP was progressively shifted upward with a maintained slope as the severity of orthostatic stress was increased (Fig. 3), and the weak relation between these two variables was maintained under mild and moderate levels of orthostatic stress. Our results therefore suggest that in humans the cardiopulmonary baroreceptors may play important roles in the modulation of the strength of MSNA bursts under orthostatic stress.

During mild orthostatic stress, the relation between total MSNA and DAP was shifted upward (with no change in slope) from that observed in control, and it was further shifted upward during moderate orthostatic stress (Fig. 4, Table 3). Total MSNA is dependent on burst number and burst strength and represents the level of MSNA more accurately than either of these elements alone (9, 10, 26, 29, 32, 38, 40). No examination has yet been made of the effect of orthostatic stress on the underlying relation between the modulation of ABR control of the occurrence and strength of MSNA bursts, on the one hand, and the modulation of ABR control of overall MSNA (total MSNA), on the other. During mild orthostatic stress, the upward shift in the linear regression line for total activity vs. DAP would be a consequence of upward shifts in the relation between burst incidence and DAP and between burst strength and DAP. During moderate orthostatic stress, the relation between burst incidence and DAP showed no further significant shift upward from the relation observed during mild orthostatic stress, and so the increase in the strength of the MSNA bursts would appear to be the main cause of the further upward shift in the relation between total activity and DAP (vs. the relation observed during mild orthostatic stress). These results suggest that, in humans, ABR modulation of efferent sympathetic nerve traffic is progressively reset to a higher level of sympathetic activity as the severity of orthostatic stress increases and that the mechanisms underlying the upward resetting of ABR control of MSNA may differ between mild and moderate orthostatic stress.
sympathetic nerve activity under orthostatic stress

Limitations. To evaluate ABR control of MSNA, we examined the spontaneous fluctuations in DAP and MSNA. There are several limitations attached to this approach. Although a linear relation between the spontaneous fluctuations in MSNA and DAP has been demonstrated in previous studies (8, 11, 13, 33, 34), the spontaneous blood pressure fluctuations are not particularly large, and so the ABR stimulus-response range that can be examined by this method is limited (within 20 mmHg). Although this is a narrower range than those obtained using other methods, such as the neck-chamber technique (10, 25, 41) or invasive pharmacological manipulation (8), a 20-mmHg change in blood pressure is within the physiological range and should be a good reflection of ABR control of MSNA under physiological conditions. Furthermore, to investigate the reflex effect elicited when two or more inputs are summed (e.g., arterial and cardiopulmonary baroreceptor inputs in this study), it is important to use inputs that are small enough not to cause saturation of the output (due to any inherent limitations in the effector responses of the system) (30). On that basis, our experimental results can be taken to reveal a physiological modulation of ABR control of MSNA during orthostatic stress. 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 ABR control of MSNA would have been small.

In conclusion, our results show that, in human subjects, ABR control of MSNA burst incidence, strength, and total activity is modulated under orthostatic stress. 1) During mild orthostatic stress, the linear relation between burst incidence and DAP was shifted upward from that observed in the control situation, but the further shift observed during moderate orthostatic stress (vs. mild orthostatic stress) was only marginal. 2) The relation between burst strength and DAP was shifted upward during mild orthostatic stress (vs. control) and further shifted upward during moderate orthostatic stress. 3) The relation between total activity and DAP was progressively shifted upward as LBNP was increased. These results suggest that, in humans, ABR-mediated beat-by-beat control of MSNA is modulated during orthostatic stress and that the modulation of this control may differ between mild and moderate orthostatic stress.

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