

Pathophysiology of orthostatic hypotension after bed rest: paradoxical sympathetic withdrawal

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Kamiya, Atsunori, Daisaku Michikami, Qi Fu, Satoshi Iwase, Junichiro Hayano, Toru Kawada, Tadaaki Mano, and Kenji Sunagawa. Pathophysiology of orthostatic hypotension after bed rest: paradoxical sympathetic withdrawal. *Am J Physiol Heart Circ Physiol* 285: H1158–H1167, 2003. First published April 24, 2003; 10.1152/ajpheart.00965.2002.—Although orthostatic hypotension is a common clinical syndrome after spaceflight and its ground-based simulation model, 6° head-down bed rest (HDBR), the pathophysiology remains unclear. The authors' hypothesis that a decrease in sympathetic nerve activity is the major pathophysiology underlying orthostatic hypotension after HDBR was tested in a study involving 14-day HDBR in 22 healthy subjects who showed no orthostatic hypotension during 15-min 60° head-up tilt test (HUT) at baseline. After HDBR, 10 of 22 subjects demonstrated orthostatic hypotension during 60° HUT. In subjects with orthostatic hypotension, total activity of muscle sympathetic nerve activity (MSNA) increased less during the first minute of 60° HUT after HDBR (314% of resting supine activity) than before HDBR (523% of resting supine activity, $P < 0.05$) despite HDBR-induced reduction in plasma volume (13% of plasma volume before HDBR). The postural increase in total MSNA continued during several more minutes of 60° HUT while arterial pressure was maintained. Thereafter, however, total MSNA was paradoxically suppressed by 104% of the resting supine level at the last minute of HUT ($P < 0.05$ vs. earlier 60° HUT periods). The suppression of total MSNA was accompanied by a 22 ± 4 -mmHg decrease in mean blood pressure (systolic blood pressure < 80 mmHg). In contrast, orthostatic activation of total MSNA was preserved throughout 60° HUT in subjects who did not develop orthostatic hypotension. These data support the hypothesis that a decrease in sympathetic nerve activity is the major pathophysiological factor underlying orthostatic hypotension after HDBR. It appears that the diminished sympathetic activity, in combination with other factors associated with HDBR (e.g., hypovolemia), may predispose some individuals to postural hypotension.

baroreflex; cardiovascular deconditioning; muscle sympathetic nerve activity

ALTHOUGH ORTHOSTATIC HYPOTENSION is a common clinical syndrome after spaceflight (2, 4, 9, 17, 34) and the ground-based simulation model of 6° head-down (HD)

bed rest (HDBR) (1, 7, 14, 15, 27, 30), the pathophysiology of the syndrome remains unclear. It cannot be explained as a simple consequence of hypovolemia induced by real or simulated microgravity because restoration of plasma volume does not improve the condition (1). In general, maintenance of blood pressure in the upright position is dependent on increases in sympathetic nerve activity (5, 29). In addition to acute sympathetic activation in response to orthostatic stress, the ability to sustain orthostatic sympathetic activation has an important role in the overall maintenance of blood pressure. Despite sympathetic activation at the onset of the orthostatic stress, sudden sympathetic withdrawal to total disappearance has been shown to cause orthostatic hypotension in patients with neurally mediated syncope (24, 25). However, the effects of real and simulated microgravity on the ability to sustain orthostatic sympathetic activation are not fully understood.

Although earlier studies (15, 17, 27, 30) have investigated increases in sympathetic nerve activity occurring in response to orthostatic stress [i.e., head-up (HU) tilt (HUT) and lower body negative pressure (LBNP)] after spaceflight and after HDBR, none have specifically addressed the time course of sympathetic nerve activity during progressive orthostatic hypotension. An early study showed that HDBR did not alter the sympathetic response to mild (30°) HUT (5 min) but that it diminished the sympathetic response to 60° HUT (5–10 min) in patients with orthostatic hypotension. However, only average MSNA and blood pressure throughout the 60° HUT were reported (30). Although recent studies (17) from the NeuroLab space shuttle mission have assessed sympathetic responses to orthostatic stress during and after spaceflight, none of the crew exhibited orthostatic hypotension or presyncopal symptoms. It is thus difficult to draw conclusions about the mechanism(s) of postflight orthostatic intolerance from these data.

Because hypotension after spaceflight and HDBR usually occurs several minutes after the onset of ortho-

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static stress rather than at its onset (2, 7, 9, 34), it would appear worthwhile to examine the changes in sympathetic nerve activity that occur during the progressive fall in blood pressure. Our hypothesis is that a decrease in sympathetic nerve activity is the major pathophysiology underlying the orthostatic hypotension seen after HDBR. To investigate this hypothesis, we designed a study involving 14-day HDBR and measured muscle sympathetic nerve activity (MSNA) during 60° HUT before and after HDBR. The aim was to elucidate the time course of MSNA in relation to orthostatic hypotension after HDBR. In addition, baroreflex function would be evaluated before and after HDBR because this is thought to control MSNA.

METHODS

Subjects. The study subjects were 22 healthy male volunteers with a mean age of 23 ± 1 yr (range 19–32). None of the subjects were smokers or users of recreational drugs, and none had chronic medical problems. All subjects were evaluated as healthy based on a detailed medical history, physical examinations, resting electrocardiography, blood chemistry results, and psychological testing. None showed signs or symptoms of orthostatic hypotension during a 15-min 60° HUT. All subjects gave their informed consent to participate in the study, which was approved by the Ethical Committee of the National Space Development Agency of Japan and the Committee of Human Research, Research Institute of Environmental Medicine, Nagoya University.

Protocols. Each subject underwent 14 days of strict adherence to HDBR in the 6° HD position. During HDBR, staff nurses continuously monitored the subjects to ensure that they remained in the HD position without interruption and performed no physical exercise. Dietary intake was restricted to between 2,000 and 2,100 kcal per day (55% carbohydrate, 25% fat, and 20% protein) and fluid intake from daily drinks was ad libitum; the average was $1,222 \pm 54$ ml per day. The photoperiod was 16 h of light and 8 h of darkness, with lights on at 7 AM. The consumption of caffeine-containing and alcoholic beverages was strictly prohibited throughout the experiment.

Two to three weeks before and immediately after the HDBR period, the hemodynamic state, baroreflex function, and orthostatic function of each subject was assessed at least 3 h after food intake. Before the pre-HDBR assessment, the subjects refrained from caffeine for 24 h and from strenuous exercise for 3 h. The experimental room was air conditioned at a temperature of 26°C.

Measurements. Blood samples were obtained from the antecubital vein in the supine position and the percent change in plasma volume with HDBR was estimated from the hematocrit level according to the method previously described by Van Beaumont (33). Central venous pressure (CVP) was measured from peripheral venous pressure by using the method of Gauer and Sieker (10). The CVP was estimated as the venous pressure measured from a catheter inserted into the large antecubital vein of the right arm, with subjects lying in the right lateral decubitus position and the right arm extended downward. Direct monitoring of central venous pressure was not undertaken because it was judged by the Committee of Human Research (Research Institute of Environmental Medicine, Nagoya University) to be too invasive and stressful for these healthy subjects while undergoing

strict adherence to 14 days of HDBR. The CVP was measured in a separate test period from the remaining data.

Arterial blood pressure was measured continuously with a pneumatic finger cuff (Portapres, TNO Institute of Applied Physics Biomedical Instrumentation) (35). Electrocardiogram (chest lead II) and thermistor respirogram readings were also recorded continuously.

MSNA was measured as reported previously by our laboratory (19). Briefly, a tungsten microelectrode (model 26-05-1, Haer; Bowdoinham, ME) was inserted percutaneously into the muscle nerve fascicles of the tibial nerve at the right popliteal fossa. The subjects did not undergo anesthesia during this procedure. Nerve signals were fed into a preamplifier (Kohn Instruments; Nagoya, Japan) with two active band-pass filters set between 500 and 5,000 Hz, and these were monitored through a loudspeaker. MSNA was identified according to the following discharge characteristics: 1) pulse synchronous spontaneous efferent discharges, 2) afferent activity being induced by tapping of the calf muscles (not by gently touching the skin), and 3) enhancement during phase II of the Valsalva maneuver. The MSNA signal was stored on a data recorder (model PC216Ax, Sony Magnascale) at a sampling rate of 12,000 Hz, along with other cardiovascular variables. The MSNA signal was full-wave rectified and fed through a resistance-capacitance low-pass filter with a time constant of 0.1 s to obtain the mean voltage neurogram. MSNA bursts were identified and their burst area calculated with the use of a computer program in the laboratory. MSNA was expressed as both the rate of integrated activity per minute (burst rate) and the total integrated activity for each individual burst area per minute (total MSNA). Because the burst area and, hence, the total MSNA were dependent on electrode position, they were expressed as an arbitrary unit that was normalized by the individual control value during supine rest; the average MSNA burst area during supine rest was given an arbitrary value of 100. The burst area for each burst during the experimental procedures was normalized by this value.

Assessment of orthostatic and baroreflex function. First, arterial and cardiopulmonary baroreflex function were assessed in a random order at a 15-min interval. Arterial baroreflex control of MSNA was assessed with the use of the Valsalva maneuver in the supine position, in keeping with previous studies (14, 20). The maneuver was performed at an expiratory pressure of 40 mmHg, with a straining period of 20 s. One to two weeks before the pre-HDBR assessment, each subject was required to practice the Valsalva maneuver to produce a >15-mmHg reduction in diastolic arterial pressure during early phase II. In pre- and post-HDBR assessments, the data for assessment of arterial baroreflex were used only when the maneuver achieved a >15-mmHg reduction in diastolic arterial pressure. Arterial baroreflex gain was defined as the slope of the least-squares linear regression of the MSNA burst area on beat-to-beat diastolic arterial pressure when MSNA significantly ($P < 0.05$) and negatively correlated with diastolic arterial pressure with $r^2 > 0.5$ (where r is a correlation coefficient) (14, 20). According to earlier studies (4, 5, 14, 20), we used diastolic arterial pressure because the strength of MSNA bursts is known to correlate closely with diastolic arterial pressure, whereas there is no significant correlation between MSNA and systolic pressure (31).

Cardiopulmonary baroreflex control of MSNA was assessed by 10° HUT and HD tilt (HDT) tests according to the previous study (32). First, subjects lay on the tilt table in the right lateral decubitus position with the right arm extended

downward. The tilt table was set at the 0° horizontal position for 20 min and was then declined to the 10° HUT position. Thereafter, it was inclined to the 0° horizontal and 10° HUT positions. The tilt table remained in each position for 5 min. CVP was measured during the 10° HUT and HDT test. In the second part of this assessment, subjects lay on the tilt table in the supine position. MSNA was measured during the 10° HUT and HDT test, using the same protocol as for the estimation of CVP. A scatterplot depicting MSNA (burst rate and total activity) over CVP was prepared by combining the two stages of the tilt test. The cardiopulmonary baroreflex gain was defined as the slope of the least-squares linear regression of MSNA on CVP during the 10° HUT and HDT test, when MSNA significantly ($P < 0.05$) and negatively correlated with CVP with $r^2 > 0.5$.

Next, 15 min after these assessments of baroreflex function, orthostatic function was assessed by 60° HUT. Electrocardiographic recordings, blood pressure, respiration, and MSNA were continuously monitored. After >10 min of supine rest, the tilt table was inclined to 60° in a passive manner and fixed for 15 min. The HUT was terminated, and the tilt table was returned to the 0° horizontal position when any of the following were observed: 1) the development of presyncopal symptoms, such as nausea, sweating, yawning, pallor, or dizziness; 2) a drop in systolic blood pressure of >20 mmHg that was sustained over 10 consecutive heartbeats; or 3) a progressive reduction in systolic blood pressure to <80 mmHg.

Statistical analysis. Data are expressed as means \pm SE. The effects of the HDBR on variables were evaluated by repeated-measures analysis of variance. When the main effect or interaction term was found to be significant, post hoc multiple comparisons were made using the Scheffé's *F*-test. The $P < 0.05$ level of difference was considered statistically significant.

RESULTS

Orthostatic responses. In the pre-HDBR assessment, all 22 subjects completed 15 min of 60° HUT without any signs or symptoms of orthostatic hypotension. After HDBR, 10 of the 22 subjects experienced orthostatic hypotension with symptoms of presyncope that warranted termination of 60° HUT testing (Fig. 1). The duration of the HUT in these subjects was 0–5 min in three subjects, 5–10 min in four subjects, and 10–15 min in three subjects.

In the subjects with orthostatic hypotension, the 60° HUT increased total MSNA to 523% of the resting supine level during the first minute of HUT before HDBR. However, the increase in total MSNA was attenuated to 314% of the resting supine level after HDBR ($P < 0.05$ vs. before HDBR; Fig. 1). HDBR tended to also attenuate the increase in total MSNA during the first minute of HUT in the subjects without orthostatic hypotension (Fig. 1).

In the subjects with orthostatic hypotension, the postural increase in total MSNA continued during the following initial minutes of 60° HUT while the arterial pressure was maintained. However, total MSNA was suppressed by 104% of the resting supine level at the last minute of HUT ($P < 0.05$ vs. earlier 60° HUT periods) in these subjects. This sympathetic suppression was accompanied by a 22 ± 4 -mmHg decrease in

mean blood pressure. In contrast, in subjects without orthostatic hypotension, activation of total MSNA was maintained throughout the 60° HUT. Figure 2 shows the time course of blood pressure and MSNA with the postural change from 0° supine to 60° HUT posture in a typical subject with orthostatic hypotension after HDBR.

In both groups of subjects, increases in heart rate during the first minute of 60° HUT were greater after HDBR than before HDBR ($P < 0.05$). Absolute levels of heart rate were higher throughout the 60° HUT after HDBR than before.

Resting hemodynamics and baroreflex functions. HDBR reduced estimated plasma volume by $13 \pm 2\%$ in subjects with orthostatic hypotension ($P < 0.01$), and by $12 \pm 1\%$ in those without ($P < 0.01$). HDBR decreased estimated CVP in the 0° horizontal position by 3.7 ± 1.0 and 4.0 ± 1.0 mmHg in subjects with and without orthostatic hypotension, respectively ($P < 0.01$ vs. before HDBR).

In 21 of the 22 subjects, Valsalva maneuvers before and after HDBR produced the required >15-mmHg reductions in diastolic arterial pressure, increasing MSNA burst area during early phase II. MSNA burst area was shown to significantly ($P < 0.05$) and negatively correlate with diastolic arterial pressure, with a correlation coefficient less than -0.7 . Therefore, the data from 21 subjects were used for assessment of arterial baroreflex before and after HDBR. Data from the remaining subject (without orthostatic hypotension), who demonstrated only a 4- to 5-mmHg reduction in diastolic arterial pressure before and after HDBR, were excluded. HDBR did not change the least-squares linear regression slope of MSNA burst area on diastolic arterial pressure in subjects with and without orthostatic hypotension, indicating that HDBR did not alter arterial baroreflex gain (Fig. 3). There was no between-subject group difference in the gain either before or after HDBR.

Both before and after HDBR, 10° HUT decreased CVP and increased MSNA (burst rate and total activity), whereas conversely 10° HDT increased CVP and decreased MSNA (burst rate and total activity) (Fig. 4). Although HDBR did not affect changes in CVP, it attenuated changes (the increase and decrease) in MSNA (burst rate and total activity) in subjects with and without orthostatic hypotension ($P < 0.05$; Fig. 4). In all trials before and after HDBR, the MSNA (burst rate and total activity) significantly ($P < 0.05$) and negatively correlated with CVP, with a correlation coefficient of less than -0.7 . Interestingly, HDBR attenuated the slope of the least-squares linear regression of MSNA (burst rate and total activity) on CVP in both groups of subjects, suggesting that HDBR attenuated cardiopulmonary baroreflex gain ($P < 0.05$, Fig. 4). The reduction in gain was evident when MSNA was expressed in burst rate as well as in total MSNA [the gain for MSNA burst rate correlated with the gain for total MSNA ($r = 0.87$, $P < 0.01$)]. There was no between-subject group difference in the gain either before

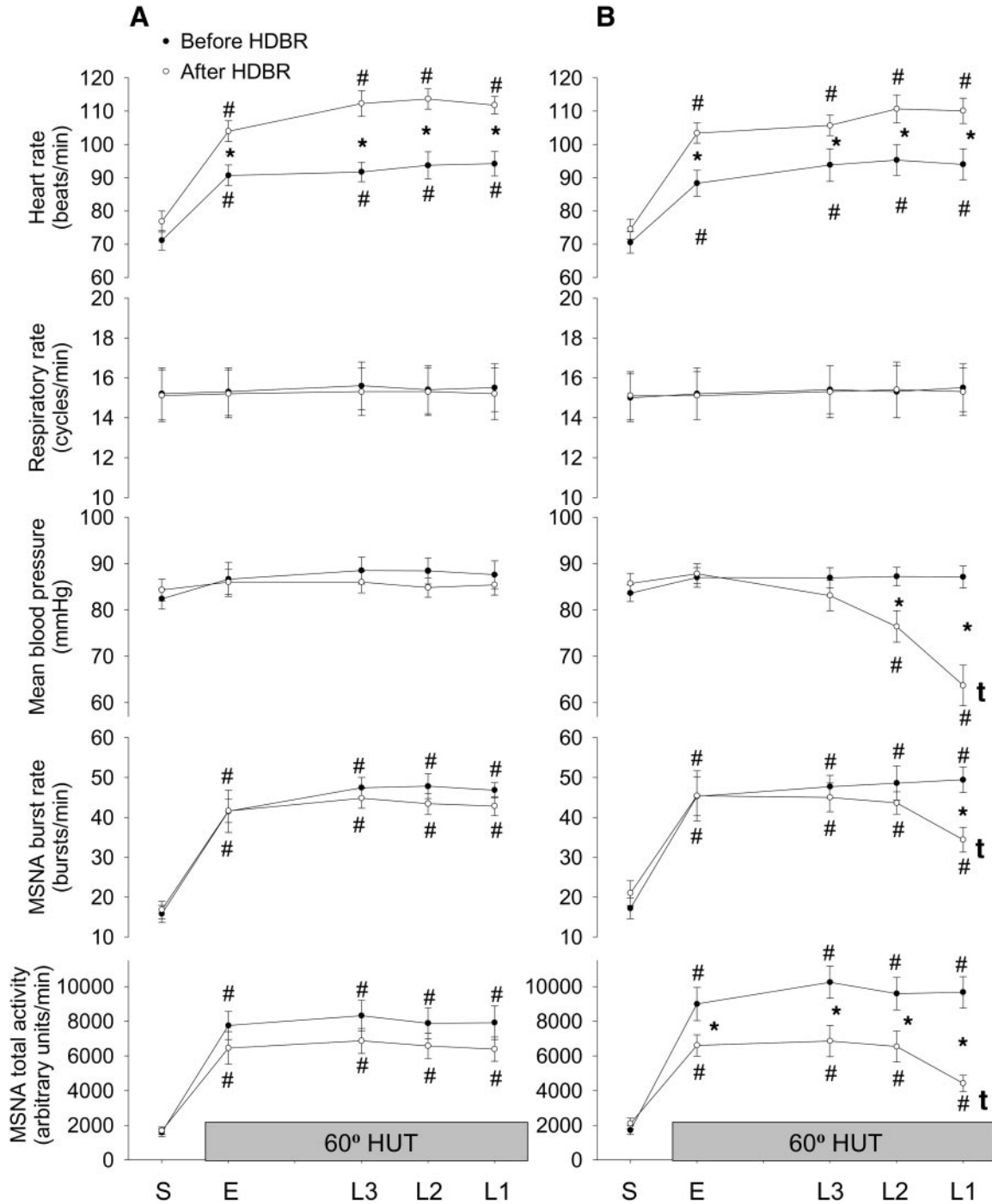


Fig. 1. Heart rate, mean blood pressure, burst rate of muscle sympathetic nerve activity (MSNA), and total MSNA during 60° head-up tilt (HUT) test in subjects after head-down (HD) bed rest (HDBR). *A*: data for subjects with progressive orthostatic hypotension. *B*: subjects without progressive orthostatic hypotension. S, supine rest; E, early phase (the first minute) of HUT; L3, L2, and L1, late phases of HUT (3, 2, and 1 min, respectively, before termination of HUT). Error bars denote means \pm SE. #*P* < 0.05 vs. supine rest; **P* < 0.05 vs. before HDBR; †*P* < 0.05, E vs. L3, L2, and L1.

or after HDBR. Mean blood pressure and heart rate were unchanged with the 10° HUT and HDT both before and after HDBR.

Significant correlations were observed between the orthostatic increase in total MSNA during the first

minute of 60° HUT and the cardiopulmonary baroreflex gain and also between these changes and HDBR (Fig. 5). No such correlation was observed between the orthostatic response in MSNA and the arterial baroreflex gain or between these changes and HDBR.

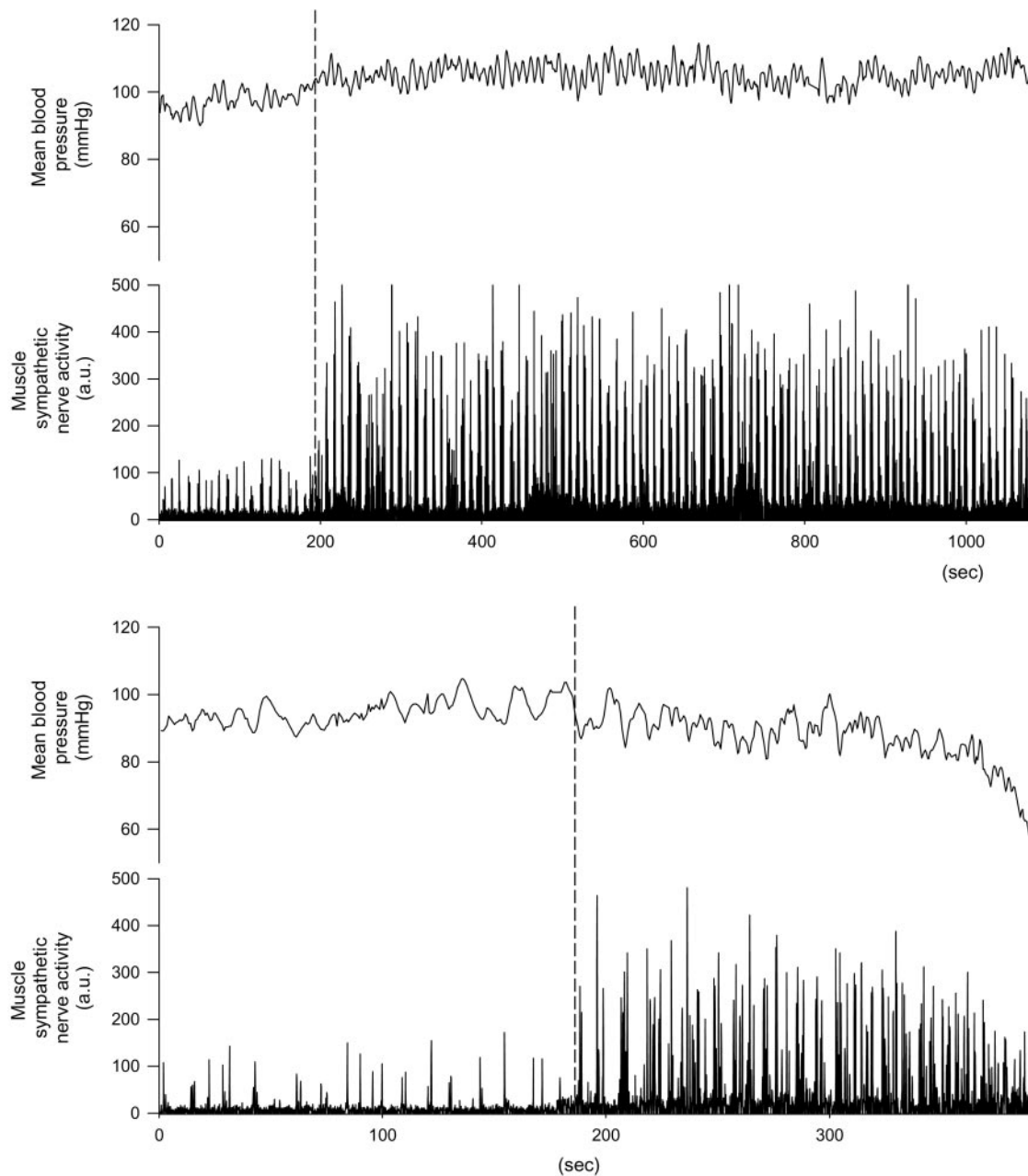


Fig. 2. Time course of mean blood pressure and MSNA trace during 0° supine rest (3 min) and 60° HUT before (*top*) and after (*bottom*) HDBR in a typical subject with orthostatic hypotension after HDBR (dotted lines indicate the onset of 60° HUT). Before HDBR, MSNA was activated in response to 60° HUT, and the activation was maintained throughout 60° HUT. Mean blood pressure was preserved throughout 60° HUT. After HDBR, although the postural activation of MSNA was reduced, the activation was maintained and mean blood pressure was preserved over several minutes. Thereafter, MSNA was mildly suppressed and this was accompanied by orthostatic hypotension to the presyncopal level (systolic pressure <80 mmHg). a.u., Arbitrary units.

DISCUSSION

To investigate the pathophysiology of orthostatic hypotension after exposure to microgravity, we examined supine and orthostatic hemodynamics and cardiovascular neural regulation before and after 14-day HDBR. Ten of twenty-two subjects experienced orthostatic hypotension after HDBR. Even in those subjects with orthostatic hypotension after HDBR, orthostatic acti-

vation of MSNA was preserved and arterial pressure was preserved during the initial minutes of 60° HUT. However, MSNA (burst rate and total activity) was paradoxically suppressed at the last minute of HUT. This suppression of MSNA was accompanied by a 22 ± 4 -mmHg decrease in mean blood pressure (systolic blood pressure <80 mmHg). In contrast, for those subjects without hypotension, orthostatic activation of

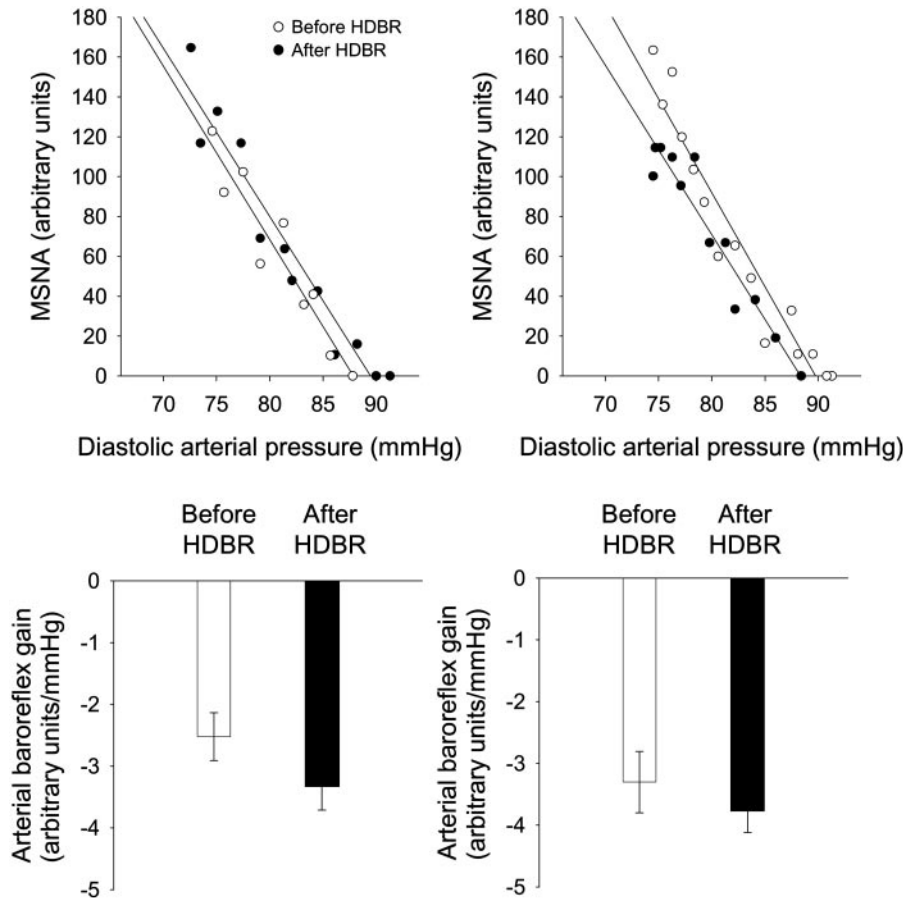


Fig. 3. *Top* graphs show the relationship between diastolic blood pressure and MSNA during early phase II of the Valsalva maneuver in representative subjects with progressive orthostatic hypotension (*top right*) and without progressive orthostatic hypotension (*top left*) after HDBR. *Bottom* bar graphs show arterial baroreflex gains assessed as the slope of the regression lines of MSNA on diastolic arterial pressure in subjects with progressive orthostatic hypotension (*bottom right*) and without progressive orthostatic hypotension (*bottom left*). The traces represent linear regression lines before and after HDBR. Open and solid bars represent values before and after HDBR, respectively. Error bars denote means \pm SE.

MSNA (burst rate and total activity) was preserved throughout the entire period of 60° HUT. These data support the hypothesis that a decrease in sympathetic nerve activity is the major pathophysiology underlying orthostatic hypotension after HDBR.

Major pathophysiology of orthostatic hypotension after HDBR: paradoxical withdrawal of MSNA. This is the first report addressing the time course of MSNA dynamics during progressive orthostatic hypotension after HDBR. Although earlier studies (14, 15, 17, 27, 30) assessed MSNA response to orthostatic stress (i.e., HUT and LBNP), none of these studies showed the time course of MSNA during progressive orthostatic hypotension, with mean blood pressure and MSNA level during orthostatic stress only reported (15, 17, 27, 30). Furthermore, recent studies from the NeuroLab space shuttle mission assessed MSNA responses to orthostatic stress during and after spaceflight. However, none of the crew exhibited orthostatic hypotension or presyncopal symptoms (17). Because orthostatic hypotension after spaceflight and HDBR occurs several minutes after the onset of orthostatic stress (2, 7, 9, 34), it is important to examine the time course of MSNA during the progressive fall of blood pressure to further understand the pathophysiology involved. In the present study, it was found that in orthostatic hypotension occurring after HDBR, MSNA was paradoxically suppressed despite its initial excitatory response to HUT.

Although the suppression of MSNA appears to be the major pathophysiology underlying the orthostatic hypotension seen after HDBR, it should be noted that the suppression observed was mild. The total MSNA during the hypotensive episode was still >210% of the supine level. This is in contrast to the pathophysiology of neurally mediated syncope, where MSNA totally disappears preceding a hypotensive episode (24, 25). The suppression of MSNA after HDBR alone appears too limited to be responsible for the hypotension seen. Thus it appears plausible that the suppression of MSNA combines with other factors associated with HDBR predisposing some individuals to orthostatic hypotension seen. Indeed, exposure to spaceflight and HDBR has been shown to induce hypovolemia (7, 34), cardiac atrophy (18), and an increase in venous compliance (26). In addition, it has been shown that compensatory augmentation of the MSNA excitatory response to orthostatic stress does not occur in all subjects in the presence of hypovolemia (14, 15, 17, 27, 30). These cardiovascular and sympathetic changes may cause hemodynamic instability under orthostatic stress after real and simulated microgravity. Under these conditions, even mild suppression of MSNA may give rise to orthostatic hypotension.

Although the paradoxical suppression of MSNA seems the major pathophysiology underlying the orthostatic hypotension observed after HDBR, we cannot rule out some other stimulus eliciting the sympathoin-

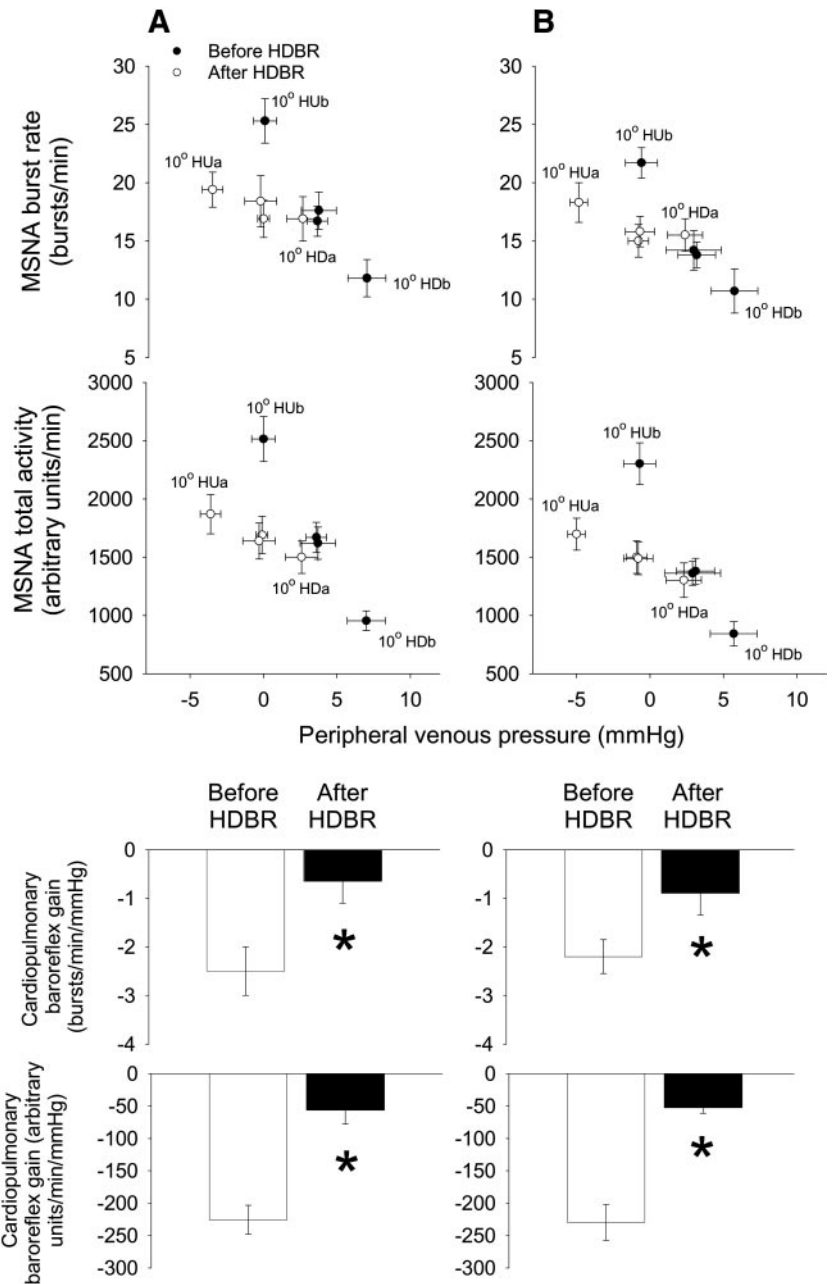


Fig. 4. *A*: hypotension (-); *B*: hypotension (+). Estimated central venous pressure (CVP), burst rate of MSNA, and total MSNA during supine rest and 10° HUT and 10° HD tilt (HDT) before and after HDBR. 10° HUb, before HDBR; 10° HUa, after HDBR; 10° HDb, before HDBR; 10° HDa, after HDBR. *Bottom*: cardiopulmonary baroreflex gains assessed as the slope of the regression lines of MSNA on CVP using burst rate and total MSNA before and after HDBR. Error bars denote means ± SE. **P* < 0.05 vs. before HDBR.

hibition. For example, some mechanical and chemical stimulations of cardiac afferents are known to inhibit sympathetic nerve activity (11). Further study will be necessary to address this point.

Compromised orthostatic activation of MSNA after HDBR. Given post-HDBR hypovolemia, the activation of total MSNA in response to orthostatic stress is possibly diminished in association with orthostatic hypotension after HDBR. In keeping with earlier studies (2, 9, 30), we observed that the postural increase in total MSNA in response to 60° HUT was attenuated after HDBR in subjects with evident orthostatic hypotension. This attenuation seems to be of great interest, given that the HDBR caused hypovolemia (13% loss of plasma volume and 3.7-mmHg reduction in estimated

CVP), which has been reported as leading to a strong augmentation of MSNA in response to orthostatic stress (16). Even in subjects without orthostatic hypotension, the orthostatic activation of MSNA may also be compromised after HDBR. It is because these subjects showed slightly attenuated (statistically unchanged) increases in total MSNA in response to 60° HUT after HDBR, despite a 12% reduction of plasma volume. These data are consistent with earlier studies on HDBR and the NeuroLab space shuttle mission, which showed unchanged orthostatic activation of MSNA in response to HUT in subjects who did not suffer from orthostatic hypotension (15, 17, 27).

Baroreflex control of MSNA after HDBR. Because orthostatic activation of MSNA depends on arterial

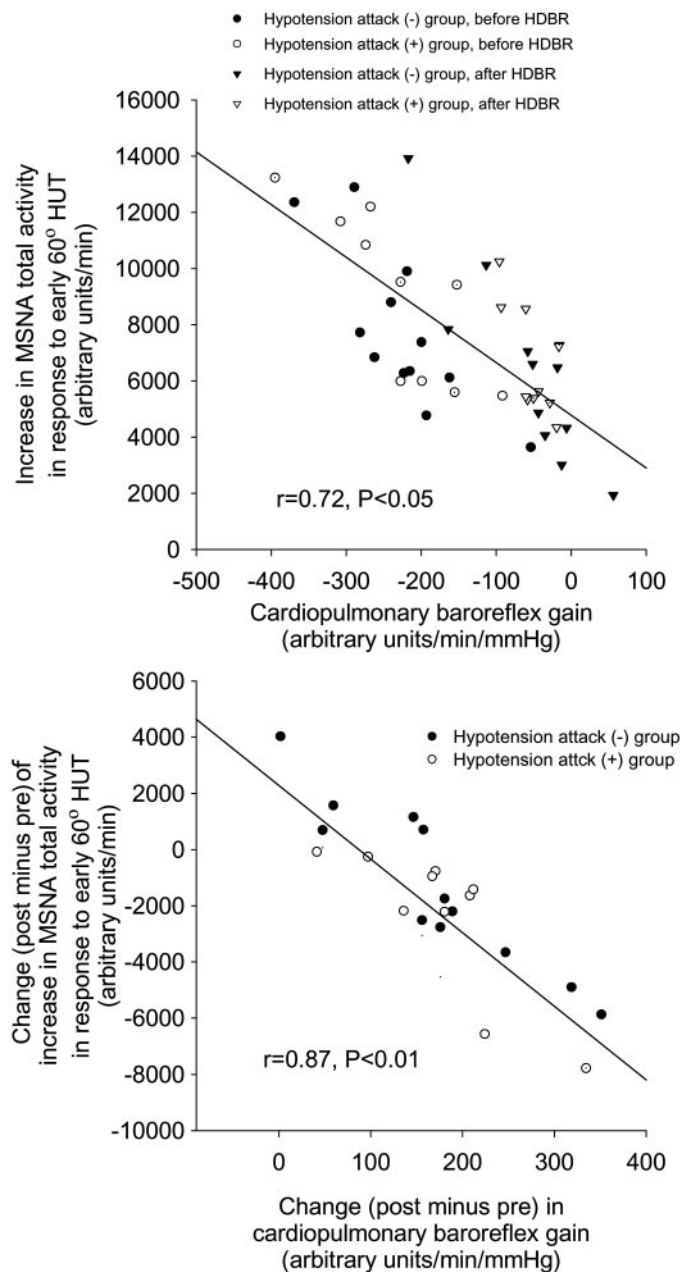


Fig. 5. Scatterplots illustrate the relationship between the orthostatic increase in MSNA during the first minute of 60° HUT and the cardiopulmonary baroreflex gain (*top*) and between these changes and HDBR (*bottom*). The traces represent linear regression lines.

and cardiopulmonary baroreflexes (5, 29), a compromised MSNA response to 60° HUT after HDBR may reflect impaired baroreflex function. Thus, before and after HDBR, both arterial and cardiopulmonary baroreflex function were assessed using the Valsalva maneuver and 10° HUT and HDT tests, respectively. Given that all noninvasive testing for baroreflex function in humans is limited in its specificity and predictive power, it is not possible to offer a definitive comment on changes in baroreflex function as a result of HDBR. However, the data obtained suggest that HDBR may attenuate cardiopulmonary, but not arterial, baroreflex gain.

Valsalva maneuver. Although the Valsalva maneuver causes an increase in MSNA burst area during early phase II, this increase is likely mediated by arterial, not cardiopulmonary, baroreflex function, because the Valsalva maneuver reduces arterial pressure while keeping central venous pressure elevated by ~40 mmHg during early phase II (28). The maneuver thus appears to unload arterial baroreceptors while loading cardiopulmonary baroreceptors. The increases in MSNA burst area seen in the study could thus result from the unloading of arterial baroreflex function.

The present results suggest that HDBR did not change arterial baroreflex gain for MSNA. In keeping with previous HDBR studies (14), HDBR did not affect the MSNA response to diastolic arterial pressure reduction (the least-squares linear regression slope of MSNA burst area on diastolic arterial pressure) during early phase II of the Valsalva maneuver. The results are also consistent with recent findings from the NeuroLab space shuttle mission (4). Accordingly, the present data, together with earlier studies, indicate that HDBR does not alter arterial baroreflex gain for MSNA.

Further studies using other assessment techniques are necessary to obtain conclusive data on the effects of HDBR on arterial baroreflex function in humans. In particular, because an assessment using the Valsalva maneuver does not provide a full profile of baroreflex static characteristics, the upper and/or lower plateaus of sympathetic level are not known. In addition, studies of hindlimb unloading, a simulation model of microgravity in rodents, have demonstrated a reduction of arterial baroreflex gain in rats (12, 21) with changing central processing of baroreceptor afferent information (22).

Ten degree HUT and HDT test. Although 10° HUT increased burst rate and total activity of MSNA, whereas 10° HDT decreased these MSNA, these MSNA responses may be partially due to arterial baroreflex function, but primarily reflect cardiopulmonary baroreflex effects. Ten-degree HUT decreased CVP, whereas 10° HDT increased CVP. That is, 10° HUT unloaded, whereas 10° HDT loaded, cardiopulmonary baroreceptors. In contrast, these tilt tests did not change finger arterial pressure. Moreover, they did not produce a reflex change in heart rate (tachycardia and bradycardia) that would theoretically be expected with arterial baroreflex unloading and loading (5). Therefore, it would seem that the stimulation of arterial baroreceptors was below threshold level.

In contrast to the normal MSNA response to the Valsalva maneuver, a novel finding of the current study was that HDBR greatly attenuated the MSNA (burst rate and total activity) response to the 10° HUT and HDT tests. This finding raises the possibility that HDBR attenuated cardiopulmonary baroreflex gain for MSNA. Indeed, cardiopulmonary baroreflex gain was assessed while total MSNA responses to changes in venous pressure were attenuated by 75% after HDBR. Because HDBR did not change arterial baroreflex gain, the potential influence of the arterial baroreflexes, if

any, on the estimation of cardiopulmonary baroreflex function would have been similar both before and after HDBR. As such, the attenuation in cardiopulmonary baroreflex gain is thought to reflect true change as a result of HDBR. In addition, the attenuation in the postural response of total MSNA with HDBR closely correlated with changes in cardiopulmonary, not arterial, baroreflex gain (Fig. 5). This finding suggests a possible contribution of cardiopulmonary baroreflex function to the compromised postural excitation of sympathetic nerve activity (23).

The present finding of attenuated cardiopulmonary baroreflex control of MSNA after HDBR is in contrast to two earlier studies showing that HDBR augmented an increase in MSNA (27) and vascular resistance (3) in response to reductions in pulmonary capillary wedge pressure (27) and CVP (3). Although we cannot explain the discrepancy between these studies and our own, it may reflect methodological differences. First, these earlier studies used -30 mmHg (27) and -20 mmHg (3) of LBNP in their assessment, whereas we employed 10° HUT and HDT tests. The LBNPs used in earlier studies appear to have activated arterial baroreceptors as well as cardiopulmonary baroreflexes as evidenced by changes in heart rate observed (27) because mild stimulation of cardiopulmonary baroreflexes does not affect heart rate, whereas arterial baroreflexes have a powerful influence on heart rate (13). In contrast, because the 10° HUT and HDT tests in the present study did not affect heart rate, they might not stimulate arterial baroreceptor function. Second, this study observed that HDBR caused orthostatic hypotension in 45% of subjects during 60° HUT and reduced HUT tolerance overall from 15 to 7.9 min. In contrast, one earlier study (27) reported only a small reduction in LBNP tolerance from 23.9 min before HDBR to 21.1 min after HDBR. Therefore, it might be argued that the effects of HDBR on cardiovascular function were somewhat limited in that study.

Although HDBR reduced cardiopulmonary baroreflex control of MSNA, the amount of reduction seen did not predict orthostatic intolerance after HDBR. HDBR reduced the cardiopulmonary baroreflex gain in subjects without orthostatic hypotension as well as those with orthostatic hypotension. This is not inconsistent with our finding that orthostatic intolerance after HDBR was associated with the attenuated maintenance of orthostatic activation of MSNA because the role of baroreflex sensitivity in sustaining sympathoexcitation has not been addressed to our knowledge. These findings, together with the finding that HDBR did not change arterial baroreflex gain as assessed by the Valsalva maneuver, suggest that these short-term baroreflex tests for MSNA are limited in their ability to predict prolonged orthostatic activation of MSNA and orthostatic intolerance after HDBR.

Burst rate and total activity of MSNA. Although we expressed MSNA as burst rate and total activity, these two measures appear to lead to the same interpretation of data. First, the paradoxical MSNA suppression during the last HUT period in subjects with orthostatic

hypotension was also observed in MSNA burst rate. Second, the post-HDBR attenuation of cardiopulmonary baroreflex gain seen was also evident when MSNA was expressed as the burst rate. The gain for MSNA burst rate closely correlated with that for total MSNA. Therefore, it appears that both evaluations of MSNA indicate similar sympathetic pathophysiology.

Limitations. Although we estimated the percent change in plasma volume from the hematocrit according to the methods of Van Beaumont (33), this method could lead to bias in the estimation of the change in plasma volume because 14-day HDBR would decrease red cell mass (8). This methodology was selected as the Evans blue dye method (6) was not approved for use by the Committee of Human Research, Research Institute of Environmental Medicine, Nagoya University. Of note, however, the magnitude of plasma volume reduction after HDBR in the present study (12–13% of pre-HDBR level) was very similar to that of other studies using the Evans blue dye method (3, 27). Therefore, we believe that the present data reflect the true changes occurring in plasma volume.

In conclusion, this study indicates that in orthostatic hypotension after HDBR, MSNA is paradoxically suppressed despite its initial excitatory response to HUT and that this suppression is closely accompanied by a reduction in arterial pressure to the presyncopal level. The data support the hypothesis that a decrease in sympathetic nerve activity is the major pathophysiology underlying orthostatic hypotension after HDBR. In addition, the data suggest that the diminished sympathetic activity, in combination with other factors associated with HDBR (i.e., hypovolemia), may predispose some individuals to postural hypotension.

DISCLOSURES

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