Contributions of MSNA and stroke volume to orthostatic intolerance following bed rest

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Shoemaker, J. K., C. S. Hogeman, and L. I. Sinoway. Contributions of MSNA and stroke volume to orthostatic intolerance following bed rest. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R1084–R1090, 1999.—We examined whether the altered orthostatic tolerance following 14 days of head-down tilt bed rest (HDBR) was related to inadequate sympathetic outflow or to excessive reductions in cardiac output during a 10- to 15-min head-up tilt (HUT) test. Heart rate, blood pressure (BP, Finapres), muscle sympathetic nerve activity (MSNA, microneurography), and stroke volume blood velocity (SVV, Doppler ultrasound) were assessed during supine 30° (5 min) and 60° (5–10 min) HUT positions in 15 individuals who successfully completed the pre-HDBR test without evidence of orthostatic intolerance. Subjects were classified as being orthostatically tolerant (OT, n = 9) or intolerant (OI, n = 6) following the post-HDBR test. MSNA, BP, and SVV during supine and HUT postures were not altered in the OT group. Hypotension during 60° HUT in the post-bed rest test for the OI group (P < 0.05) was associated with a blunted increase in MSNA (P < 0.05). SVV was reduced following HDBR in the OI group (main effect of HDBR, P < 0.02). The data support the hypothesis that bed rest-induced orthostatic intolerance is related to an inadequate increase in sympathetic discharge that cannot compensate for a greater postural reduction in stroke volume.

Doppler ultrasound; head-up tilt; muscle sympathetic nerve activity; presyncope

IN NORMAL INDIVIDUALS blood pressure (BP) is maintained during orthostatic stress by reflex-mediated increases in heart rate (HR) and total peripheral resistance (TPR) that compensate for the gravitational reduction in venous return and stroke volume (6). The role of sympathetic constriction in maintaining BP during orthostatic stress is apparent from observations of severe orthostatic hypotension in individuals with autonomic failure and other syndromes affecting sympathetic outflow (16, 17, 21, 25). However, the mechanism(s) producing orthostatic difficulties in otherwise healthy individuals with intact sympathetic nervous function remains unclear.

Many healthy individuals with no history of orthostatic hypotension demonstrate difficulties in standing up following short-term (8) and longer-term bed rest (10, 29) and spaceflight (4, 15). Recent studies indicate that the inadequate increase in TPR in those subjects who could not complete a 10-min stand test following spaceflight (4) might be related to diminished norepinephrine release (15). However, this hypoadrenergic response to upright posture could be due to a reduced sympathetic nerve activity or increased norepinephrine clearance. Animal studies point to diminished baroreflex control of sympathetic neural discharge during a hypotensive stimulus (20). The effects of bed rest on sympathetic neural responses to orthostatic stress are not known.

On the other hand, some investigators have argued that altered cardiac function is a critical determinant of the reduced tolerance for postural stress following bed rest or spaceflight (18, 35). However, a direct relationship between altered cardiac function and orthostatic intolerance has not been clearly defined.

In this study we have made direct measures of muscle sympathetic nerve activity (MSNA) and stroke volume blood velocity (Doppler ultrasound) to investigate the contributions of changes in cardiovascular versus sympathetic factors associated with bed rest-induced orthostatic intolerance. With these methods we investigated the hypothesis that altered orthostatic tolerance with head-down tilt bed rest (HDBR) was related to inadequate sympathetic outflow (4, 15).

METHODS

Subjects

Sympathetic and cardiovascular responses to orthostatic stress vary between men and women (9). Also, the magnitude of sympathoexcitation during postural stress varies with the menstrual phase (26), leading to difficulties in interpreting the effects of 14 days of bed rest on sympathetic responses to orthostatic stress in women versus men. Therefore, in the current study we report data obtained from 15 male volunteers from whom successful nerve recordings were obtained during both the pre- and post-bed rest tests of orthostatic tolerance. No evidence of orthostatic intolerance was observed in these volunteers in the pre-HDBR study. The mean age of this group was 28.2 ± 8.2 (SD) yr (range 18–46 yr). All subjects were healthy as determined by a comprehensive medical questionnaire and history, a complete physical examination, and an electrocardiogram. The subjects were nonsmokers and had a body mass index of 24.5 ± 3.2 (SD) kg/m². All subjects provided signed consent for the experimental procedures on a form that had been approved by the Institutional Review Board at the Milton S. Hershey Medical Center.

Bed Rest

During the 14-day bed rest period the subjects were monitored constantly and were strictly confined to bed in the −6° head-down position. They were not allowed to stand or sit but could rise on one elbow to eat. Each day the photoperiod was 16 h of light, with lights on at 0700. Vital signs of BP, HR,
and oral temperature were assessed four times daily at 4-h intervals while the subjects were awake. Body weight was assessed every other day. During the HDBR the average daily caloric intake for the subjects was ~2,500 kcal, which consisted of ~55% carbohydrate, 25% fat, and 20% protein. Daily dietary sodium intake was ~3,000 mg. Fluids were allowed ad libitum, but the subjects were encouraged to consume >2,000 ml/day.

Experimental Tilt Procedure

Tilt studies of orthostatic tolerance were performed ~14 days prior to the commencement of the bed rest period and again on day 14 of HDBR. Each subject reported to the laboratory no less than 2 h after a light meal. Each subject had abstained from caffeine for 24 h before the pre-HDBR test, and no caffeine was allowed during the HDBR period. For each tilt test baseline measures of MSNA (5 min) and cardiovascular (2 min) indexes were collected after the subject had rested quietly for 15–30 min following instrumentation. Subsequently, the subject was passively tilted (2°/s) to 30° of head-up tilt (HUT) for 5 min followed by a period of 60° HUT. The duration of the pre-HDBR 60° HUT test was 5 min in the initial three subjects and 10 min for 12 subjects. The initial 30° HUT period was used to assess if changes in cardiovascular responses to this mild level of stress would be predictive of any orthostatic intolerance that developed during 60° HUT (21). Twelve subjects were supported by an adjustable seat on the tilt table, whereas three subjects supported their own weight on the left leg; the right leg from which MSNA data were obtained was always flexed and did not support weight. The test protocols for each subject were the same in each of the pre- and post-bed rest tests.

Continuous measures of HR, electrocardiogram (ECG), arterial BP (finger plethysmograph, Finapres; Ohmeda, Englewood, CO), ascending aorta stroke volume velocity (SVV), and peroneal nerve MSNA were collected at baseline and during the transition to each level of tilt. The finger from which BP was recorded was maintained at heart level throughout the tilt procedure. Ascending aorta blood velocity was recorded from the suprasternal notch using a 2-MHz pulsed-wave Doppler probe (Multigon, Yonkers, NY) with the depth adjusted so that the velocity signal was obtained from a region ~1–2 cm above the aortic valves. The probe position was adjusted slightly between the supine and upright postures to compensate for shifts in heart position and thereby maintain optimal strength of the auditory and visual Doppler shift signal. An analog signal of the instantaneous mean SVV was produced by demodulation of the quadrature signal. The average SVV was quantified by determining the area under the mean velocity curve over 60 s while supine and over ~10 cardiac cycles during HUT. The same time periods were used to obtain the average HR and BP responses during supine and HUT postures.

MSNA was recorded from the peroneal nerve of the unloaded right leg using the microneurographic technique (33) as described previously for our laboratory (27). A 200-µm diameter, 35-mm long tungsten microelectrode that was tapered to an uninsulated 1- to 5-µm tip was inserted transcutaneously into the peroneal nerve just posterior to the fibular head. A reference electrode was positioned subcutaneously 1–3 cm from the recording site. Neuronal activity was amplified 1,000 times by a preamplifier and 50–100 times by a variable gain isolated amplifier. The signal was band-pass filtered with a bandwidth of 700–2,000 Hz and then was rectified and integrated to obtain a mean voltage neurogram. A MSNA site was confirmed by manually manipulating the microelectrode until the characteristic pulse-synchronous burst pattern was observed that increased in frequency during a voluntary apnea but did not change in response to arousal or produce skin paresthesias (11).

The signals for ECG, BP, MSNA, and SVV were sampled at 100 Hz and stored on a dedicated computer using a commercially available data acquisition system (Power Lab, ADI Instruments, Castle Hill, New South Wales, Australia).

Data Assessment

The baseline HR, BP, and mean blood SVV were recorded from all cardiac cycles over at least 2 min. HR, BP, and SVV responses during HUT were determined from the average over 10–15 consecutive cardiac cycles at the end of each tilt level (28). An index of cardiac output (COi) was calculated as \[ \text{SVV (cm/s)} \times \text{HR (beats/min)}. \] An index of TPR (TPRi) was calculated as mean arterial pressure/COi. It was assumed that the aortic valve orifice dimensions were not changed by the bed rest intervention. The MSNA neurogram was quantified according to the burst frequency of each minute during the baseline and tilt phases of the study. Because HR changes with bed rest the MSNA response was also quantified as bursts/100 heart beats (burst incidence).

Baseline MSNA was averaged over 5 min.

Orthostatic intolerance was defined as 1) HR > 135 beats/min, 2) sudden hypotension > 20 mmHg reduction in systolic or diastolic BP with or without bradycardia that was sustained over 10 consecutive heart beats, 3) episodic systolic BP oscillations of > 20 mmHg, and 4) symptoms such as nausea, dizziness, yawning, sweating, pallor, visual disturbances, and/or muscle weakness. After the post-HDBR test the subjects were grouped as those who were orthostatically tolerant (OT, n = 9) or orthostatically intolerant (OI, n = 6). The OI group was comprised of four individuals who did not complete the post-HDBR test because of presyncopal episodes. In addition, two subjects finished the post-HDBR HUT test but displayed symptoms consistent with orthostatic intolerance.

Statistical Analysis

The effect of HDBR and time during the tilt test on the cardiovascular responses to HUT for the OT group was analyzed using a repeated measures two-way analysis of variance procedure with SAS statistical software (SAS Institute, Cary, NC). Tukey’s post hoc analysis was used to further examine specific point-wise comparisons. P < 0.05 were considered statistically significant, and all values are reported as means ± SE.

RESULTS

When all subjects are grouped together the mean supine HR was increased in the post (70 ± 2 beats/min)- compared with the pre (63 ± 2 beats/min)-HDBR condition (P < 0.05). Body weight was not different on the pre (77.0 ± 2.6 kg)- and post (77.6 ± 2.9 kg)-bed rest test days.

MSNA Responses

There were two features that differentiated the OT and OI groups following bed rest. First, baseline MSNA burst frequency and burst incidence were increased ~50% following bed rest in the OI group (P < 0.05) compared with no change in the OT group (Fig. 1). Second, greater MSNA values in the OI group were maintained during 30° HUT but not during 60° HUT;
end tilt levels of MSNA burst frequency were similar in both groups following bed rest. This resulted in a blunted increase in burst frequency (Fig. 2) and total MSNA (Fig. 3) during the post-bed rest response for the OI group at 60° HUT ($P < 0.05$). For the OT group the increase in both nerve burst frequency and total MSNA on going from 0° to 30° and from 30° to 60° of HUT was not changed by the bed rest period. Complete MSNA data for one subject in each of the OI and OT groups were not available as the nerve recording site was lost on going from 30° to 60° of HUT in each of the pre- and post-bed rest tests. However, eliminating these subjects from the data analysis did not alter the observation of a significantly elevated baseline MSNA and blunted HUT response in the OI group.

**Cardiovascular Responses**

OT group. The effect of bed rest on cardiovascular responses at rest and during HUT for the OT group are shown in Fig. 4. As expected, HR increased and SVV decreased ($P < 0.0001$) on going from supine to 30° and 60° HUT. Compared with pre-bed rest, CO in the post-bed rest test tended to be greater ($P < 0.06$) following the higher supine and HUT HR ($P < 0.05$) and an unaltered SVV response. Compared with su-
pine, systolic BP during 30° and 60° HUT was augmented in the post- but not the pre-HDBR test (P < 0.05). Diastolic BP was increased above baseline during 60° (P < 0.0001) HUT in the pre-HDBR test and during 30° and 60° HUT during the post-HDBR trials. TPRi increased during 60° HUT both before and following HDBR (P < 0.05).

OI group. The cardiovascular responses of the OI group to HUT with HDBR are shown in Fig. 5. Unlike the OT group, supine HR was not significantly increased in the OI group. Nonetheless, the HR response to HUT was greater following bed rest (P < 0.0001). Of note, the increase in HR (ΔHR) above baseline at 60° HUT for the OI group (41 ± 4 beats/min) was greater than for the OT group (29 ± 3 beats/min; P < 0.002). Compared with pre-HDBR, SVV was lower in the post-HDBR tilt test (HDBR main effect, P < 0.02). The difference in absolute levels of SVV at 60° HUT approached the level of statistical significance (P < 0.08). The COi was not different in the two tests.

In contrast with the OT group, only diastolic BP increased above supine levels during 60° HUT in the pre-HDBR test (P < 0.004, Fig. 5). However, significant systolic (P < 0.0001) and diastolic (P < 0.0005) hypotension was observed during 60° HUT following HDBR. TPRi did not increase in the OI group during either the pre- or post-HDBR tilt test.

DISCUSSION

The mechanism(s) of diminished orthostatic tolerance in susceptible individuals following bed rest and/or spaceflight is unclear. Current evidence points to either a reduction in cardiac stroke volume (18) or to a diminished vasoconstrictor response (4). The diminished postural vasoconstriction has been related to altered end-organ constrictor responses (12) and/or to reductions in norepinephrine release (15). In turn, the subnormal release of norepinephrine may be related to reductions in sympathetic nerve discharge following central alterations in sympathetic control (20).

For the OT subjects the 14-day HDBR period did not change the MSNA, SVV, or BP responses to HUT. Therefore, this group was resistant to the cardiovascular deconditioning effects of prolonged inactivity. Several important observations differentiated the subjects who demonstrated orthostatic intolerance from those who did not follow bed rest. In contrast to the OT group, OI individuals did not significantly elevate TPRi in either the pre- or post-HDBR tests. This may have been due to the smaller number of subjects in the OI group because the same increase in TPRi, observed in the OT group during the pre-HDBR test, did reach statistical significance. A second differentiating factor was the significant elevation of supine MSNA burst frequency in the OI group following HDBR. Finally, the orthostatic hypotension experienced during 60° HUT by the OI group was associated with a blunted increase in MSNA. The latter observation supports the hypothesis that the orthostatic intolerance associated with bed rest may be related to an insufficient sympathetic response. These observations raise the possibility that previous reports of inadequate increases in TPRi (4) and plasma norepinephrine levels (15) during postural stress following spaceflight are in part related to a blunted central sympathetic response. As observed in earlier examinations of neural responses in otherwise healthy individuals who become presynaptic during progressive HUT tests (21) there was no apparent effect of HDBR on the MSNA or cardiovascular responses to 30° HUT in the current study.

In addition to altered MSNA responses, cardiovascular limitations were also evident in the OI group following bed rest. Under conditions of an intact sympathetic nervous system reductions in cardiac mass (18) and blood volume (2), as well as increased venous pooling (30, 31), all may contribute to reduced stroke volume during upright posture. The mechanism for the diminished SVV in the current study is not clear. Whereas excessive venous pooling may limit venous return following spaceflight or bed rest (30, 31), some investigators have demonstrated that post-HDBR orthostatic intolerance develops in the absence of changes in dependent limb venous congestion (3, 4). Nonetheless, we do not know to what extent pooling of venous blood in the legs and visceral beds changed with the bed rest intervention. If blood volume was reduced during bed rest (14) then the proportion of blood pooled in the legs may have been greater following bed rest.

Nonetheless, the contributions of diminished blood volume and stroke volume in determining tolerance for orthostatic stress remain uncertain. Blomqvist and Stone (2) report on several studies that indicate that volume loading to compensate for venous pooling and restore central venous pressure to pre-bed rest levels did not reduce the incidence of orthostatic intolerance.
It is acknowledged, however, that possible reductions in left ventricular mass (18) may obviate any beneficial effects of volume loading on cardiac stroke volume. Importantly, Buckey et al. (4) observed that the magnitude of reduction in blood volume and stroke volume had no apparent relationship with the ability to complete a 10-min stand test following spaceflight. Furthermore, Bungo et al. (5) demonstrated that reductions in cardiac dimensions persisted for 1–2 wk following exposure to microgravity, a period of time that extends far beyond the expected reductions in orthostatic tolerance (4, 15). Finally, a similar incidence of orthostatic intolerance has been observed after only 4 h of head-down tilt before any important reductions in blood volume are likely to occur (7). Therefore, we believe that diminished cardiac function may contribute to orthostatic hypotension only if reflex mechanisms that regulate BP are inadequate.

Two mechanisms have been proposed to account for altered sympathetic nerve responses during postural hypotension. First, a hyperadrenergic condition in combination with diminished venous return may cause excessive activation of ventricular afferents that inhibit sympathetic outflow (i.e., the Bezold-Jarisch reflex) (19, 25). Second, resetting of the arterial baroreflexes may occur during a hypotensive episode leading to diminished sympathetic discharge (22, 34). The blunted MSNA despite falling BP in the current study supports the latter concept of inappropriate baroreflex resetting. This response may include central inhibition of sympathetic discharge (13). It is noteworthy that the absolute burst frequency attained during 60° HUT by both the OT and OI groups was the same in both the pre- and post-bed rest tests. It will be of interest to examine if bed rest alters the maximal attainable reflex-specific sympathetic outflow.

As indicated previously, supine MSNA burst frequency was significantly elevated in the OI group following bed rest. Whether changes in baseline sympathetic activity relate to differences in orthostatic tolerance (6) remains to be clarified. In the presence of unchanged supine arterial pressure and CO, the elevated baseline MSNA burst frequency suggests an alteration in the baroreflex and/or central control of sympathetic discharge directed to skeletal muscle. These data raise the question as to whether countermeasures that can sustain the augmented MSNA may diminish the orthostatic problems in these individuals.

In contrast with the current results, we observed a reduction in the supine MSNA burst frequency in 13 of 16 individuals following 14 days of HDBR in an earlier study (27). We did not examine the orthostatic responses of these earlier volunteers. Based on the current and previous (6) data, we speculate that a higher proportion of this earlier group would have demonstrated orthostatic tolerance following HDBR.

Methodological Considerations

The use of a support seat for the majority of subjects may have altered venous return during the HUT maneuver (1). However, if this were a problem then the incidence of OI among the 12 subjects in whom the support seat was used should have been greater than in the group for whom no such support was used. In addition, the varied duration of tilt at 60° may have precluded the opportunity to observe presyncopal events in the shorter studies. However, three of the four subjects for whom the post-bed rest tilt test was terminated became presyncopal within 5 min of 60° HUT. The proportion of subjects who demonstrated orthostatic intolerance following bed rest (6 of 15) is in line with previous studies (4, 10, 32) despite some variation in the support mechanism and duration of tilt.

Measures of SVV are indicative of changes in stroke volume if the left ventricular outflow dimensions remain relatively unchanged after HDBR. We are not aware of any reports of the effect of bed rest on aortic dimensions. Moreover, the differential effect of bed rest on cardiac morphology of OT and OI subjects is not known. Cardiac mass may be reduced following 2 wk of HDBR (18), and based on the current data it is likely that this effect would be greater in the OI group. Therefore our assumption that aortic orifice dimensions were unchanged with bed rest may underestimate the differences in cardiac output in the two groups.

Microneurographic techniques allow direct examination of sympathetic discharge. Therefore, our measures of peroneal MSNA are a general index of sympathoexcitation with HUT and how this response was affected by 14 days of HDBR. However, baroreflex control of sympathetically mediated changes in vascular resistance appears to vary among limb and visceral beds (23, 24). Although peroneal MSNA was changed with HDBR in some individuals, sympathetic outflow to other vascular beds may have been affected differently. Importantly, sympathetic constriction of visceral vessels appears to be critical for orthostatic tolerance (36). However, the current data showing that postural hypotension occurred concurrently with a blunted increase in peroneal MSNA support earlier findings that regulation of sympathetic discharge to both limb and renal beds was diminished following cardiovascular deconditioning (20).

Perspectives

Cardiovascular regulatory mechanisms are impaired in post-bed rest orthostatic intolerance. The reduction in cardiac output with upright posture must be compensated for by reflex mechanisms that increase peripheral vascular resistance. If these reflex mechanisms are inadequate then BP falls, leading to reductions in cerebral perfusion. In the current study, reflex constrictor mechanisms in the OI group were inadequate to compensate for the diminished stroke volume. It will be of interest to examine whether the blunted MSNA response despite hypotension during HUT was related to altered baroreflex control of sympathetic discharge, to central inhibition of sympathetic outflow, or to the altered baseline MSNA that precluded elevation in sympathetic constriction above a preset maximal level.
As such, these data support the hypothesis that postbed rest OI in susceptible individuals is related to an inadequate increase in sympathetic vasoconstriction that cannot compensate for the greater postural reduction in stroke volume.

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REFERENCES

