Head-up suspension in humans: effects on sympathetic vasomotor activity and cardiovascular responses

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Shamsuzzaman, A. S. M., Y. Sugiyama, A. Kamiya, Q. Fu, and T. Mano. Head-up suspension in humans: effects on sympathetic vasomotor activity and cardiovascular responses. J. Appl. Physiol. 84(5): 1513–1519, 1998.—We hypothesized that muscle sympathetic nerve activity (MSNA) and cardiovascular responses to the conventional head-up tilt (HUT) are different from those to head-up suspension (HUS) because of antigavity muscle activity. The MSNA from the tibial nerve, heart rate, blood pressure, stroke volume, cardiac output, and calf blood flow were measured in 13 healthy young subjects. Left atrial diameter was measured by two-dimensional echocardiography in another nine subjects. The resting MSNA and cardiovascular responses at a low level (20°) of orthostasis were similar during both modes. At higher levels (40 and 60°), the responses of MSNA, heart rate, stroke volume, and cardiac output were significantly stronger and there was a smaller reduction in calf blood flow during HUT than during HUS (P < 0.05). Left atrial diameter was decreased significantly from the resting values during HUT and HUS without any significant difference between the modes of orthostasis. The results provide evidence that the engagement of antigavity muscles during HUT may have additive effects on sympathetic vasoconstrictor and cardiovascular responses to orthostatic stress.

METHODS

Subjects

Thirteen healthy young male volunteers were selected for the direct recording of the efferent MSNA from the tibial nerve. The mean values for their physical characteristics were as follows: age, 32 ± 1 (SE) yr; height, 1.7 ± 0.01 m; weight, 65 ± 2 kg; and body fat, <20% of body weight. All subjects gave their informed written consent before participating in the experiment. The subjects were in good health, and they had had no history or evidence of any diseases within the 6 mo before the experiment. None was taking any medications, nor had any of them smoked or consumed caffeinated beverages or exercised on the day of the study. The procedure of nerve recording was in accordance with the guidelines of skeletal muscle pump by redistributing blood toward the central part of the body (12).

Although passive graded HUT produces only modest relaxation of the antigavity muscles of the leg, back, and abdomen, the technique has been used for many years to test the integrity of sympathetic vasomotor activity and cardiovascular control mechanisms in healthy humans and in patients with symptoms suggestive of postural hypotension or unexplained syncope. The technique applied to create orthostasis should ideally relax the antigavity muscles, because the muscle activity may alter the circulatory responses to tilt because of muscle pumping or direct stimulation of afferent nerves within the muscles. The saddle (17) and the parachute harness (23) techniques have been introduced to provide body support without weight bearing by the legs to reduce the antigavity muscle activity and its effects on cardiovascular reflexes. The saddle produces relaxation of the leg muscles, but it causes contraction of the muscles of the back and abdomen, and the subject experiences discomfort around the groin and instability at higher levels of orthostasis. The parachute harness produces relaxation of the antigavity muscles of the legs, but it necessitates a seated posture, which is not desirable. In the present experiment, a newly developed head-up suspension (HUS) technique was employed with a modified body harness to produce maximum relaxation of the antigavity muscles and simultaneous production of graded orthostatic stress.

Our hypothesis was that the efferent MSNA and cardiovascular responses to HUT are different from those to HUS because of the difference in the antigavity muscle activity. To test the hypothesis, we carried out intraneural recording of the MSNA from the tibial nerve and noninvasive measurement of the circulatory responses during passive graded HUT and during graded HUS at same levels and for same duration.
the Japan Microneurography Society, and the protocol of the procedure had been approved by the Human Research Committee of the Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan.

Recording of MSNA

Multiunit recordings of the efferent MSNA to the blood vessels of the calf muscles were obtained from the tibial nerve at the popliteal fossa by the technique of tibial microneurography. A 70-mm-long tungsten microelectrode that had 120-µm-shaft and 1-µm-tip diameters, was inserted with epoxy resin except at the last few micrometers from the tip, and had an impedance of 2–5 MΩ (Frederick Haer, Brunswick, ME) was used for this purpose. The course of the tibial nerve at the popliteal fossa was marked on the skin with low-voltage transcutaneous electrical stimulation. A reference surface electrode was pasted on the skin surface 2–3 cm away from the site of the recording electrode. The microelectrode was inserted manually through the intact skin into the tibial nerve, without the use of any local anesthetics. The electrode-tip position within a muscle nerve fascicle leading to the calf muscles was identified by the appearance of afferent spindle activity elicited by tapping or stretching the calf, whereas light skin touch on the calf did not elicit such response, and the sympathetic origin of the neural discharge was identified by the spontaneous and pulse-synchronous rhythmic bursts of neural activity that were accentuated markedly during the Valsalva maneuver but not during presentation of arousals such as loud noise (7, 15). Then minor adjustments of the electrode position were made until the characteristic pattern of multiunit bursts of the efferent MSNA with a high (>3 dB) signal-to-noise ratio was obtained. The nerve signals were amplified with a preamplifier (MEG-1251, Nihon Kohden, Tokyo, Japan) and passed through 500- to 5,000-Hz band-pass filters (E3201A, NF, Yokohama, Japan) to increase the signal-to-noise ratio. The amplified and filtered signals were then rectified and integrated at a time constant of 0.1 s to obtain a mean voltage display of the multiunit neural activity. The integrated neurogram was monitored continuously with a loudspeaker and an oscilloscope and was recorded on paper for manual counting. MSNA was quantitated as the burst rate (number of bursts/min) and burst incidence (number of bursts/100 heartbeats).

Respiration, Heart Rate (HR), and BP

Respiration was monitored with a thermistor (ZE-732 A, Nihon Kohden) to detect any changes in respiration such as apnea or tachypnea. HR changes were recorded continuously by ECG. Indirect arterial BP was measured by two different methods: intermittently (every minute) from the brachial artery with an automatic sphygmomanometer and continuously with a Finapres BP monitor (CBM 7000, Ohmeda, Louisville, CO) to record the BP at the finger held at heart level. The mean BP of the brachial artery was calculated as the diastolic BP plus one-third pulse pressure.

SV, CO, and Calf Blood Flow (CBF)

Thoracic impedance (Zt) and impedance waveforms (dz/dt) were measured intermittently by using an impedance plethysmograph (A1–601G, Nihon Kohden) and a differentiator (ED 601 G, Nihon Kohden). Two pairs of self-adhesive aluminum tape electrodes were attached around the neck and around the trunk at the level of the xiphisternum. Two other pairs were wrapped around the calf and lower part of the leg just above the ankle joint, contralateral to the nerve recording limb. The dZ/dt was recorded intermittently at the end of the resting period and at each level of orthostatic stress for 10 consecutive heartbeats, with breath holding at the end of expiration, to avoid respiration-related variations of thoracic Zt and dZ/dt. The SV was calculated from the change in the dZ/dt associated with the ventricular ejection time (ET), the baseline thoracic Zt, and the distance between the recording electrodes (L) by using the following equation: SV = \rho × (L/Zt) \times dZ/dt × ET, where ρ is the specific resistivity of blood, which was assumed to be 135 Ω/cm (14, 21). CO was calculated by multiplying the SV by the instantaneous HR. CBF was measured using a noninvasive occlusive method, similar to the method for measuring SV (9).

Antigravity Muscule Activity

The electromyogram (EMG) of two antigravity muscles of the nerve recording limb, the tibialis anterior and soleus, were monitored continuously throughout the experiments.

Echocardiographic Measurements

An additional group of subjects was selected for the two-dimensional echocardiographic measurement of left atrial (LA) diameter to demonstrate the effect of orthostatic stress on the engagement of cardiac baroreceptors. The study group consisted of nine healthy male volunteers, ages 20–39 yr. They were in good health, they had had no history of any diseases, and none was taking medications. The two-dimensional echocardiography was performed with a 3.5-MHz ultrasound transducer and imaging system (SSA-270A, Toshiba Medical Systems, Tokyo, Japan). The ECGs were recorded on S-VHS videotapes with a videocassette recorder (SVO-9500 MD, Sony) during the experiment, and measurements were made after the completion of the experiments. All the results of echocardiographic measurements were printed on paper (Super Sonoprinter TP-810, Toshiba). An ECG was recorded and displayed simultaneously to allow for timing of intracardiac events. The LA diameters were measured by M-mode recording of the LA in the standard parasternal long-axis view. Both the systolic and diastolic diameters of LA were measured. The diastolic diameter was measured at the onset of QRS signal of ECG or after mitral valve closure in the ECG and corresponded to the smallest atrial diameter. The systolic diameter was the largest atrial diameter that could be recorded at the end of ECG T wave or at the beginning of the mitral valve opening in the echocardiogram. For each body position three echocardiographic views were measured, by using the Leading Edge to Leading Edge technique (20), and the mean was used in the statistical analysis. The ECG results were read blinded. Of nine subjects, data from two subjects were excluded from the result due to incomplete recording in one subject and vasovagal reaction in the other.

Postural Maneuvers

Orthostatic stress was applied by the conventional HUT technique and by HUS. The former was used to provide a graded orthostatic stress with contraction of the antigravity muscles and was produced by tilting the bed gradually, with a footboard positioned so that the subject stood on it. The newly developed HUS was used as a graded orthostatic stimulus without the engagement of the antigravity muscles. A body harness (TROLL), originally for use by mountain climbers for safety during climbing, was modified by covering the belt with a soft pad to ease the pressure discomfort and was used to produce HUS. Briefly, after the subjects rested in a horizontal supine position for 15 min on a tilt bed, the
shoulder straps of the harness were connected with the head end of the bed by two ropes, strong enough to support the weight of the subject. The footboard of the tilt table was then removed, and the bed was gradually tilted to 20, 40, and 60° to cause the subject to be suspended from the head end of the tilt bed without any contact of his feet with the footboard or the floor.

Protocols

The experiments were carried out in an artificial climate chamber with an ambient temperature of 25°C and relative humidity of 40%. The artificial climate chamber was activated at least 30 min before the experiment to bring the temperature and humidity to the desired level. The subject arrived at the laboratory at 9 AM after an overnight fast or at 3 PM after a light lunch at noon. After he had emptied his bladder, his height and weight were measured. Skinfold thickness at four sites was measured with a Lange skinfold caliper to estimate the amount of total body fat. The subject was fitted with the modified body harness and then lay horizontally in the supine position on the tilt bed. The instruments for the recording of all the variables except neurogram were set in place. After instrumentation and familiarization to the room environment, the subject practiced the HUT and HUS procedures. While the subject rested in the supine horizontal position, we searched for the recording site of the tibial nerve at the popliteal fossa, and the microelectrode was inserted into the muscle nerve fascicle as described earlier. After we obtained an acceptable recording of the MSNA, the subject rested in the supine horizontal position in the quiet environment for 15 min, while the MSNA and cardiovascular parameters were recorded. The orthostatic stresses were applied for three consecutive, sequential 5-min periods at the levels of 20, 40, and 60°. Each subject completed both modes of orthostatic stress (HUT and HUS) in the same experimental session. The sequence of orthostatic stresses was chosen randomly so that in one-half of the studies the orthostatic stress by HUT was completed first. The two stress modes were separated by at least 10 min of supine recovery period. Each subject completed both modes of orthostatic stress (HUT and HUS), and the two stress modes were separated by at least 10 min of supine recovery period.

Data Storage and Statistics

The signals were displayed on a storage oscilloscope (VC6524, Hitachi Denshi, Tokyo, Japan) and recorded on paper (Reci-Horiz, NEC San-Ei, Tokyo, Japan). All recorded data were stored on tape (multichannel FM tape recorder, KS-616U, Sony Magnascale, Tokyo, Japan) for the subsequent analysis. Data were averaged for each 5-min period and are expressed as means ± SE. Statistical comparisons of the procedures of orthostatic stresses (HUT and HUS) were made for each variable using two-way analysis of variance (ANOVA) with repeated measures. The statistical significance of the difference between the HUS and HUT was analyzed by using paired Student's t-test. In all tests the difference was considered statistically significant when P < 0.05.

RESULTS

The subjects did not complain of any pain or discomfort because of the body harness during or after completion of HUS. Only one subject showed vasovagal reactions during HUS at 40°. The subject was brought to horizontal position immediately, and the experiment was terminated. The data for that subject are not included in the results. The hemodynamic changes for three subjects were studied for the second time ~6 mo after the first experiment and following the identical protocol but with a different sequence of orthostatic stresses. The ANOVA values showed no significant interaction between modes of orthostatic stress and between sequences of the experiment for any variable.

MSNA

A typical example of original and integrated MSNA in one subject during supine rest and 60° orthostatic stress by HUS and by HUT is shown in Fig. 1. The average resting values of MSNA burst rate and burst incidence for the HUT and for the HUS were not significantly different (Fig. 2). Orthostatic stresses at 20° by both procedures produced similar MSNA responses (Fig. 2). However, the HUT at higher levels (40 and 60°) was associated with a larger increase in the efferent sympathetic activity compared with the HUS at the same levels (Figs. 1 and 2). The values of MSNA burst rate during the passive graded HUT and during HUS at 40° (48.0 ± 2.6 and 41.6 ± 2.1 bursts/min) and at 60° (52.4 ± 3.1 and 48.4 ± 2.8 bursts/min) were significantly different (HUT vs. HUS; P < 0.05; Fig. 2). Significant differences were also observed between HUT and HUS (P < 0.05; Fig. 2) for the MSNA burst incidence at 40° (65.7 ± 3.9 and 59.3 ± 3.2 bursts/100 heartbeats) and at 60° (66.3 ± 4.4 and 64.8 ± 4.7 bursts/100 heartbeats).

Cardiovascular Responses

HR. The resting HR during HUT and HUS and the responses at 20 and 40° were similar. The HUT at 60° induced a more marked increase in HR compared with that produced by the HUS at the same level of ortho-
static stress (Figs. 1 and 2). The difference in HR response between HUT and HUS at 60° was statistically significant (81.7 ± 3.2 vs. 76.5 ± 2.3 beats/min; P < 0.05; Fig. 2).

BP. The resting values of BP during HUT and HUS were similar. The changes in systolic BP during HUT and HUS at all levels and the changes in diastolic and mean BP at 20 and 40° were also similar. However, slight but significant differences between HUT and HUS at 60° for mean BP (84 ± 2.1 and 87 ± 2.7 mmHg) and for diastolic BP (66 ± 2.3 and 70 ± 2.7 mmHg) were observed (HUT vs. HUS; P < 0.05, Fig. 2).

SV, CO, and CBF. The resting values of SV, CO, and CBF during HUT and HUS were similar. There were reductions in SV and CO at each level of orthostatic stress for both modes of stress. However, the reductions in SV and CO were larger during HUT at 60° than during the HUS at the same level. The differences between HUT and HUS at 60° for the reduction in SV (49.6 ± 3.3 and 48.3 ± 2.5 ml/heartbeat) and in CO (3.16 ± 0.14 and 3.40 ± 0.15 l/min) were statistically significant (HUT vs. HUS; P < 0.05; Fig. 3). The CBF was reduced less during HUT at higher levels, and the differences between HUT and HUS at 40° (4.24 ± 0.26 and 3.49 ± 0.19 ml·min⁻¹·100 ml⁻¹) and at 60° (3.62 ± 0.26 and 3.12 ± 0.25 ml·min⁻¹·100 ml⁻¹) were statistically significant (HUT vs. HUS; P < 0.05, Fig. 3).

LA dimension. The resting systolic and diastolic diameters of LA during HUT (30.28 ± 1.2 and 18.24 ± 1.42 mm) and during HUS (28.78 ± 0.21 and 17.96 ± 0.42 mm) were similar. Both systolic and diastolic diameters of the LA during HUT at 60° (22.4 ± 1.2 and 14.34 ± 1.42 mm) and during HUS at 60° (23.3 ± 1.46 and 15.56 ± 1.3 mm) were significantly reduced from the control values (Fig. 4; P < 0.05). However, the difference in the LA diameter between HUT and HUS was not statistically significant.

Antigravity Muscle Activity

The EMG recording of the soleus and tibialis anterior did not disclose any activity during the supine rest.
period and during the HUS at any levels of orthostasis. A typical example of EMG activity in one subject during supine rest, 60° HUS, and 60° HUT is shown in Fig. 1. The changes in posture by HUT produced an immediate and transient increase in the EMG activity of the antigravity muscles. There was only a slight and consistent increase in the EMG activity throughout the HUT at 60° (Fig. 1).

**DISCUSSION**

The orthostatic stress by HUT induced gravity-dependent distribution of extracellular fluid toward the lower part of the body and unloading of low- and high-pressure baroreceptors that accentuated sympathetic vasoconstrictor activity (3, 22). This activity is an important factor in redistribution of blood flow to the vital organs and in the maintenance of cardiovascular homeostasis during orthostatic stress. In addition to the baroreflex-mediated responses, the existence of a muscle-heart reflex has been suggested in cats (10, 16) and in humans during steady-state exercise (2) and active standing (4, 5, 8, 11). However, the effects of antigravity muscle activity on the sympathetic vasoconstrictor activity during erect posture in humans are not yet known.

The present study was designed to elucidate the role of antigravity muscle activity on the sympathetic vasoconstrictor and cardiovascular responses during orthostatic stress. Two different techniques were used to employ orthostasis along with or without engagement of the antigravity muscles; the conventional passive graded HUT and HUS with the body harness did not produce any activity of the antigravity muscles during orthostatic stress. By comparing the responses to both techniques of orthostatic stress, the influence of the antigravity muscles on the sympathetic neural activity...
and cardiovascular responses were determined. The changes in posture by graded HUT and HUS induced progressive increase in sympathetic vasoconstrictor outflow to the skeletal muscle vascular bed and HR because of progressive reduction in the SV and CO with increasing levels of orthostatic stress (from supine to 20, 40, and 60°). The changes by HUT are comparable to those observed in the previous studies (6, 13, 18, 22). However, the responses in MSNA and HR during HUS at higher levels (40 and 60°) were significantly lower than during HUT at the same levels and duration (Fig. 1).

The antigravity muscle activity was reported even during quiet standing, and this activity may modulate the cardiovascular function during erect posture in humans (12). The EMG activities of the two antigravity muscles of the leg, the soleus and tibialis anterior, were monitored throughout our experiments and showed no activity during HUS and a slight but consistent increase in the EMG activity during HUT (Fig. 1). Thus the greater responses of MSNA and cardiovascular variables to HUT may suggest that the potential for sympathoexcitation to baroreceptors unloading increases with the engagement of antigravity muscles.

The MSNA responses to muscle activity in humans depend on a number of factors, including the mode (isometric or rhythmic), intensity, duration, and mass of contracting muscle. The enhancement of MSNA during muscle activity is due to the reflexes originated from the contracting muscles. The existence of muscle mechanoreflex that modulates cardiovascular and respiratory functions was studied in cats (16). Later study on the same animal documented that the muscle reflex stimulates postganglionic efferents innervating the vasculature of skeletal muscle (10). Therefore, a slight but consistent increase in the EMG activity of the antigravity muscles during HUT at higher levels of orthostasis may have initiated a mechanoreflex from the contracting muscle and might have an additive effect on the sympathetic neural responses to orthostasis.

Besides the non-baroreflex-mediated (muscle afferents) effect on MSNA and HR, the antigravity muscle activity modifies CBF and, consequently, venous return to the heart and SV. Forceful contraction of the leg and abdominal muscles in standing and dynamic contraction of muscles of the lower limb result in translocation of blood from the peripheral vessels to the intrathoracic compartments (skeletal muscle pump). If the pump works properly during the passive graded HUT, SV and CO are expected to be larger than during HUS. However, both variables were unexpectedly smaller, with less reduction in the CBF during HUT. Contrary to forceful static contraction of the skeletal muscles, static contraction of human calf muscles at relatively low force increases muscle blood flow (19). There is no direct evidence on the blood-flow distribution to the calf muscles during passive graded HUT. The weak and static activity of the antigravity muscles during passive HUT may possibly cause the smaller reduction in the CBF during HUT. The larger volume of blood in the lower limb consequently produces larger the reduction in SV and CO. The alteration in the SV and CO produces a larger increase in the baroreflex-mediated MSNA responses to orthostatic stress that are observed during HUT at 60°.

Contrary to the result of SV and CO, echocardiographic measurement of systolic and diastolic diameter of the LA did not show any significant differences between HUT and HUS at 60°. The results ruled out the differences in the engagement of cardiopulmonary baroreceptor during HUT and HUS at higher levels of orthostatic stress. Therefore, the engagement of antigravity muscles during HUT may initiate a non-baroreflex-mediated reflex response and produce a higher increase in the MSNA and HR.

Additional Considerations

The results demonstrating less accentuation of MSNA and HR and a concurrent increase in the mean and diastolic BP during HUS at 60° seem to indicate that the higher BP responses might have stimulated the arterial baroreceptors and blunted the baroreceptor-mediated reflex responses to the orthostatic stress. The exact mechanisms of the higher BP responses during HUS at 60° without any increase in the MSNA are not yet known. The compression of the belt of the body harness may be considered as a probable factor. The belt compressed the tissue mainly around the upper part of the thighs. The compression may have stimulated mechanically sensitive skin and muscle afferents. Muscle compression is a prominent determinant of HR and BP (25), and the responses may be due to increase in the sympathetic vasoconstrictor activity.

The other effect of the belt is on the blood flow to the lower limb. It may impede venous blood flow only, or it may impede both the arterial and venous flow. If the former occurs, the MSNA should increase during HUS due to venous congestion and stagnation of a larger volume of venous blood in the lower limb. In the latter occurrence, the compression should be high (suprasystolic) to block the arterial and venous blood flow to the lower limb. The subjects did not feel any discomfort during HUS at any levels due to the pressure of the belt of the harness. This finding suggests that the compression effect on the lower limb blood flow, if present, would have been insubstantial.

Conclusion

HUS produced significantly less increase in MSNA and HR accompanied by smaller reduction in SV and CO at higher levels of orthostatic stress. The engagement of the antigravity muscles during HUT may have additive effects on sympathetic vasoconstrictor and cardiovascular responses to orthostatic stress.

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