Comparison of cardiovascular responses between lower body negative pressure and head-up tilt

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Submitted 1 June 2004; accepted in final form 7 February 2005

IT IS KNOWN THAT, DURING ORTHOSTATIC stress, peripheral vascular resistance and/or heart rate (HR) increase (mainly via cardiopulmonary and arterial baroreflexes), serving to maintain arterial blood pressure (1, 3–5, 7, 8, 17, 27, 36, 37, 39, 42, 44, 47). Furthermore, it has been suggested that, during orthostatic stress, differential vascular responses occur between the arms and legs (9, 12, 16). The proposed explanations for the latter phenomenon include differences in transmural pressure (11, 12, 18) modulating the local vascular response, a greater difference in vasoconstriction between the upper and lower limbs would occur in HUT than in LBNP when muscle sympathetic nerve activity (MSNA) is similar. Because no study has yet compared the vascular responses in the upper and lower limbs between LBNP and HUT, we set out to do this, and on the basis of our results we discuss the possible mechanisms responsible for the different vascular responses between the upper and lower limbs during orthostatic stress.

METHODS

Subjects. We studied 10 healthy volunteers (8 men and 2 women) with a mean age of 23 ± 1 yr, a body weight of 64.3 ± 8.0 kg, and a height of 170 ± 9 cm. The subjects were nonsmokers and normotensive, and none was taking any medication. The study was in accordance with the Declaration of Helsinki and approved by the Human Subjects Committee of the University of Tsukuba, and each subject gave informed, written consent.

Experimental protocol. Before the experiment, we familiarized each subject with the procedures by exposing them to an orientation session in which they experienced HUT and LBNP. On the experimental day, after entering the test room, which was maintained at 25°C, each subject adopted the supine position in an LBNP box that could be tilted. The waist was sealed at the level of the iliac crest. After measurements at supine rest had been completed [baseline 1 (BL1)], LBNP was applied at −20 and −40 mmHg (LBNP20 and LBNP40), each level being sustained for 3 min. After release of LBNP, recovery was allowed for at least 5 min followed by further posture, and the negative pressure affects mainly the superficial veins, less so the arteries, so arterial blood pressure is almost constant throughout the whole body. In contrast, during HUT, the arterial and venous pressures increase in proportion to the distance from the heart. Thus LBNP and HUT represent two possible ways of decreasing the central blood volume and enhancing sympathetic nervous activity, but they differ in the extent of the change in hydrostatic pressure (local pressure) in the dependent limbs. Some 35 yr ago, −40 mmHg LBNP was reported to lead to an amount of blood pooling in the lower limbs equivalent to that observed in subjects changing from the horizontal to the upright position (25). Thus, in terms of the amount of blood pooling in the lower body and the change in central blood volume, a LBNP of −20 to −40 mmHg should be almost the same as 60° HUT, suggesting that the degree of unloading of the cardiopulmonary baroreceptors could be similar between these two experimental situations.

Thus it can be hypothesized that if local mechanisms activated by increments in transmural pressure (11, 12, 18) modulate the local vascular response, a greater difference in vasoconstriction between the upper and lower limbs would occur in HUT than in LBNP when muscle sympathetic nerve activity (MSNA) is similar. Because no study has yet compared the vascular responses in the upper and lower limbs between LBNP and HUT, we set out to do this, and on the basis of our results we discuss the possible mechanisms responsible for the different vascular responses between the upper and lower limbs during orthostatic stress.

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“supine rest” measurements [baseline 2 (BL2)]. Then, subjects were tilted to 60° HUT at a rate of 1°/s. Because all the variables of interest could not be measured within a single performance of this protocol, it was repeated several times (separated by at least a 10-min recovery period). During a given performance of the protocol, we measured one of the following: 1) forearm blood flow (FBF), 2) echocardiographic measurements of left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), 3) brachial artery diameter (Dbrachial), 4) brachial artery blood flow velocity (Vbrachial), 5) femoral artery diameter (Dfemoral), or 6) femoral artery blood flow velocity (Vfemoral). FBF was measured only at BL1, LBNP20, and LBNP40. HR and blood pressure were measured throughout all experiments.

Measurements. FBF was estimated by venous occlusion plethysmography with the aid of a rubber strain gauge (46). A venous occlusion cuff around the upper arm was inflated to 40 mmHg for 10 s out of every 20 s, providing one blood flow measurement every 20 s. FBF is expressed in milliliters per deciliter per minute. Because the venous occlusion plethysmography technique is sensitive to body movements and to the initial distending pressure in veins, we measured FBF only during LBNP.

Left ventricular diameter was determined by means of two-dimensional echocardiography in five subjects (in the remaining 5 subjects, technical problems prevented measurements being made). Two-dimensional images were obtained from the left parasternal long-axis window to yield M-mode images of the left ventricle. For this, we used a transducer with a frequency of 2.5–3.5 MHz (HD3500 Ultrasound Imaging System, ATL). Data were collected on videotape for later analysis, in which we used values averaged over continuous 20 heartbeats for the last 1 min of each stage. Left ventricular volume was calculated using Teichholz’s equation (40): namely, 

\[ V = \frac{7}{3} \cdot \frac{D_s + D_d}{2} \cdot H \]

where V is left ventricular volume, and Ds and Dd are systolic and diastolic vessel diameters. We measured FBF only during LBNP.

Cardiac output (CO) was taken as the product of SV and HR. Cardiac output (CO) was taken as the product of SV and HR.

Vbrachial and Vfemoral were measured by using the Doppler technique. The Doppler ultrasound system (5–12 MHz; HDI3500 Ultrasound Imaging System, ATL) used in the present study permits beat-by-beat measurements of mean blood flow velocity (Vmean cm/s). The Doppler probes were adjusted manually over the brachial or femoral arteries by one investigator. These two velocities were measured in each experiment; however, because we had only one Doppler probe, we measured only one velocity in each protocol. The technique plethysmography) and brachial blood flow (FBfemoral; measured by the Doppler method) during lower body negative pressure (LBNP). Each value is expressed as a percentage of baseline.

RESULTS

We measured FBF by venous occlusion plethysmography and BFfemoral by the Doppler ultrasound method, and we measured FBF during both LBNP20 and LBNP40. Figure 1 shows the relationship between FBF and BFfemoral (each expressed as a percentage of its baseline value) during LBNP. A significant correlation (r = 0.92; P < 0.05) was observed between the two types of measurements. Therefore, we regarded the values obtained by the Doppler method as useful for examining reflex blood flow responses in this study.

Effects of LBNP and HUT on the central circulation. Figure 2 shows MAP and HR responses during LBNP and HUT. MAP did not change significantly from either baseline (B1 or B2) during LBNP and HUT (75 ± 2 mmHg at B1, 72 ± 2 mmHg during LBNP20, 71 ± 1 mmHg during LBNP40, 74 ± 1 at B2, and 77 ± 2 mmHg during HUT; not significant). In contrast, HR increased during both LBNP40 and HUT (57 ± 2 beats/min at B1, 71 ± 3 beats/min during LBNP40, 57 ± 3 beats/min at B2, and 68 ± 3 beats/min during HUT; P < 0.05), but it did not change significantly during LBNP20 (62 ± 2 beats/min; not significant).

Table 1 shows the results obtained by echocardiography. LVEDV, SV, and CO all decreased during LBNP and HUT (P < 0.05), with the values obtained during HUT lying between those obtained for LBNP20 and LBNP40.
CARDIOVASCULAR RESPONSES DURING LBNP AND HUT

Effects of LBNP and HUT on the peripheral circulation. BF_{brachial} and BF_{femoral} decreased from the relevant baseline level during LBNP and HUT (BF_{brachial}: 116 ± 7 ml/min at B1, 59 ± 9 ml/min during LBNP20, 49 ± 6 ml/min during LBNP40, 115 ± 12 ml/min at B2, and 66 ± 8 ml/min during HUT; P < 0.05; BF_{femoral}: 309 ± 53 ml/min at B1, 167 ± 19 ml/min during LBNP20, 122 ± 12 ml/min during LBNP40, 328 ± 55 ml/min at B2, and 101 ± 9 ml/min during HUT; P < 0.05). The increase in femoral vascular resistance was significantly greater than that in brachial vascular resistance during HUT (P < 0.05). The increase in femoral vascular resistance was significantly greater than that in brachial vascular resistance during HUT (P < 0.05), although there was no significant difference between them during either LBNP20 or LBNP40 (Fig. 5).

DISCUSSION

We compared cardiovascular responses between LBNP and HUT, and our main findings were that 1) central cardiovascular responses (changes in LVEDV, SV, and MAP) were comparable between LBNP and 60° HUT, and 2) the increases in brachial and femoral vascular resistances during LBNP were similar to each other, but 3) the relative increase in femoral vascular resistance was greater than that in brachial vascular resistance during 60° HUT. Those findings suggest that, during HUT, peripheral vascular responses in the lower limbs are augmented, presumably by local mechanisms specifically induced in the dependent limbs.

Both LBNP and HUT are known to increase the pooling of blood in the lower body, leading to decreases in both central blood volume (2, 4, 5, 30) and cardiac filling pressure (1, 3, 4, 14, 15, 17, 22, 23, 35, 42, 43, 45). Such orthostatic stresses evoke baroreflex-mediated increases in peripheral vascular resistance and HR that serve to maintain blood pressure (1, 3–5, 7, 36, 38, 39, 42, 44, 47). To evaluate the changes in central blood volume occurring during 60° HUT and LBNP in the present study, we used echocardiography to measure LVEDV, which has been used as an index of the filling of the heart (2, 21, 30). LVEDV was decreased by the three maneuvers in the following rank order: −40 mmHg LBNP > HUT > −20 mmHg LBNP. This suggests that, in terms of the central hypovolemia, the degree of orthostatic stress experienced by a subject during 60° HUT lies somewhere between those experienced during −20 mmHg LBNP and −40 mmHg LBNP and that the extent of the cardiopulmonary unloading would be in the same rank order.

Jacobsen et al. (16) reported that the changes in subcutaneous and skeletal muscle blood flows measured by the 133Xe-washout technique during −10 mmHg LBNP did not differ between arm and calf. Although Essandoh et al. noted that the decrease in blood flow (measured by strain gauge plethysmography) was much smaller in the calf than in the forearm during −20 mmHg LBNP (9) and also during the postural change from supine to sitting (10), Vissing et al. (45) later observed that the increase in vascular resistance was similar between calf and forearm during LBNP. Furthermore, in the present study, no difference was detected in the change in vascular resistance between the arm and the leg during LBNP (at either −20 or −40 mmHg). Almost 20 yr ago, Victor and Leimback (43) were the first to show that MSNA in the leg did indeed increase during LBNP, and later Rea and Wallin (34) noted similar MSNA responses between arm and leg during LBNP. Thus, if we accept that vascular and MSNA responses are quite similar between the upper and lower limbs during LBNP, the impli-

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**Table 1. Systemic hemodynamics during LBNP and HUT**

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>−20 mmHg LBNP</th>
<th>−40 mmHg LBNP</th>
<th>Baseline 2</th>
<th>60° HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV, ml</td>
<td>129±3</td>
<td>105±6*</td>
<td>81±5*</td>
<td>132±6</td>
<td>95±3*</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>42±1</td>
<td>39±4</td>
<td>30±4*</td>
<td>39±1</td>
<td>33±3</td>
</tr>
<tr>
<td>SV, ml</td>
<td>87±2</td>
<td>66±3*</td>
<td>51±2*</td>
<td>94±5</td>
<td>62±2*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>4.9±0.1</td>
<td>3.9±0.2*</td>
<td>3.5±0.2*</td>
<td>5.0±0.2</td>
<td>4.1±0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE for 5 subjects. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; CO, cardiac output; Baseline 1, measurements at supine rest before LBNP; Baseline 2, additional supine rest measurements after LBNP and before HUT. *Significant difference from relevant baseline, P < 0.05.
cation is that cardiopulmonary and arterial baroreflex unloading during LBNP leads to vasoconstrictions of similar magnitude between the upper and lower limbs.

In our comparison of vascular responses between HUT and LBNP, we found a greater response in the lower than in the upper limbs during HUT, but not during LBNP, even though the degree of central hypovolemia would be comparable between the two conditions. Although we cannot be sure of the correct explanation for this phenomenon, the following need to be considered. First, it is possible that sensitivity to sympathetic vasoconstrictor activity differs between the arm and leg in HUT. At rest, vascular resistance is reportedly greater in the legs than in the arms (13), despite regional norepinephrine spillover being greater in the arms than in the legs (13, 19). Moreover, it has been suggested that the number and/or sensitivity of α1-adrenergic receptors is greater in the legs than in the arms (26). However, if the above were the correct explanation(s) for our HUT data, we should have expected a greater vasoconstriction in the legs than in the arms during LBNP too, and this did not occur in our study.

A second possibility involves the participation of vestibular reflexes, which are activated by stimulation of the vestibular otoliths, for example, during HUT (24, 32, 33). This reflex is thought to contribute to increases in MSNA in both arm and leg. It is not known whether activation of this reflex induces a greater vasoconstrictor response in the leg than in the arm. Thus it is considered that vestibular reflexes are activated during HUT but not during LBNP. However, we have no reason to suppose that the greater vasoconstriction in the lower limb than in the upper one during HUT can be explained by the participation of this reflex.

The third possibility involves the limb vascular responses being modulated by local mechanisms. In our comparison between LBNP and HUT, the main difference between the two situations was the hydrostatic pressure to which the lower body was exposed. LBNP is usually employed with the subject in the horizontal posture, as it was here, and the change in transmural pressure affecting the arteries and veins in the lower body was, therefore, 20 or 40 mmHg at most in the present study. During HUT, due to the influence of the hydrostatic pressure, blood pressure increases in the part of the body below the heart. We measured the distances from the heart to the inguinal region and to the foot in our subjects, and we estimated the average increases in hydrostatic pressure at the inguinal region to be 27 mmHg and at the foot to be 77 mmHg during 60° HUT. Thus, although LBNP and HUT are both ways of decreasing the central blood volume and increasing blood pooling in the lower body, they differ in the magnitude of the change in hydrostatic pressure (local pressure) induced in the lower body. Therefore, we must consider that arterial and venous pressure in the dependent parts increased more during HUT than during LBNP and that, therefore, greater arterial distension and venous congestion occurred in the former than in the latter situation. In this context, we should mention the possibility of the existence of local vasoconstrictor mechanisms, as suggested by some previous investigators. Henriksen (11) found that venous distension causes arterial vasoconstriction in humans (venoarterial reflex) and considered that this reflex is activated when the transmural pressure exceeds 25 mmHg. Musgrave et al. (25) noted that the total venous pooling in the lower body was similar between HUT and −40 mmHg LBNP. However, in our study, the status of venous distension during HUT (where there is a pressure gradient from 27 mmHg at the femoral vein to 77 mmHg at the foot veins) would have been different from that during LBNP (where there is an almost constant pressure from femoral to foot veins). As yet, it is not clear to us whether this difference might affect the venoarterial reflex response in such a way as to cause a greater vasoconstrictor response in the lower legs during HUT than during LBNP. On the other hand, because the arterial pressure in the lower legs would have been higher during HUT than during LBNP, the myogenic response [in which vasoconstriction occurs when the transmural pressure increases, and vasodilation occurs when transmural pressure decreases (6, 20, 28, 29)] might have been greater in the arteries in the lower legs during HUT than during LBNP. Imadojemu et al. (12) found that, whereas MSNA responses were similar between arm and leg during 40° HUT, blood flow...
velocity decreased only in the femoral artery. Because vascular responses are usually thought to be linearly related to the increase in MSNA (45), Imadojemu and colleagues suggested that this phenomenon was due to an interaction between sympathetic nerve activity and the myogenic response. On the basis of the above discussion, we tentatively suggest that because the increase in transmural pressure in the lower limbs during HUT is greater than that during LBNP, the finding of a greater vasoconstriction in the femoral than in the brachial artery during HUT reflects a modulating influence of local mechanism(s) over the reflex vascular responses induced by unloading of the cardiopulmonary and arterial baroreceptors.

Limitations. We measured peripheral blood flow by the ultrasound Doppler technique. During LBNP and HUT, venous occlusion plethysmography, which has been used by many investigators to assess the extent of sympathetic vasoconstriction, is not suitable for measuring blood flow in the lower body because of the venous distension. Radegran (31) reported a significant correlation between individual measurements of femoral artery blood flow made simultaneously by the ultrasound Doppler method and the thermodilution technique (at rest and during incremental 1-leg dynamic knee-extensor exercise). His finding suggests that the Doppler method is suitable for measuring blood flow even during exercise, in which muscle blood flow may increase >10-fold compared with the value measured at rest. We measured BF\textsubscript{brachial} and BF\textsubscript{femoral} blood flows during LBNP and HUT, maneuvers during which the blood flow decreases, and because this is the opposite of the changes examined by Radegran, we needed to confirm the suitability of the ultrasound Doppler measurement in such a situation. What we did was to compare the change in FBF measured by venous occlusion plethysmography with that in BF\textsubscript{brachial} measured by the ultrasound Doppler technique during LBNP, and we found a significant correlation between the two types of measurements (Fig. 1). Thus arterial blood flow measurement by the ultrasound Doppler method could be as useful for studying reflex blood flow responses as venous occlusion plethysmography has been in the past.

Our measurements of BF\textsubscript{brachial} and BF\textsubscript{femoral} would include both skin and muscle blood flow, but we cannot separate these tissue blood flows by the Doppler technique. We can assume that there is a greater muscle mass in the legs than in the arms, and the total fraction of the limb made up by muscles might be greater for the leg than for the arm in our subjects. Thus, if cardiopulmonary and arterial baroreceptors modulate blood flow more powerfully in muscle than in skin, it is possible that a greater vasoconstriction occurs in the legs due to the presence of a greater muscle mass there than in the arms. However, in the present study, although a greater vasoconstriction occurred in the leg than in the arm during HUT, this did not happen during LBNP. Thus differences in the muscle fractions between leg and arm seem unlikely to explain the different responses between LBNP and HUT.

We did not consider the possibility that there might be a difference in the transmural pressure in the carotid baroreceptor region during LBNP and HUT. In the present study, although MAP did not change throughout the experiment, the blood pressure within the carotid baroreceptor region should have been somewhat lower during HUT than during LBNP, because of the lower hydrostatic pressure in the former situation. Any unloading of the carotid baroreceptors during HUT might have influenced the cardiovascular response (i.e., a further vasoconstriction might have occurred during HUT). However, such a vasoconstriction, if present, should have occurred throughout the entire body (at least in the arms and legs), and it is, therefore, difficult to explain the greater increase in femoral than in brachial vascular resistance during HUT. Furthermore, Thompson et al. (41) reported that forearm vascular resistance was unaffected by carotid baroreceptor unloading (induced by neck pressure (+10 mmHg]) during cardiopulmonary baroreceptor unloading (−20 mmHg LBNP). So, we suspect that in the present study peripheral vascular resistance would have been almost unaffected by carotid baroreceptor unloading during HUT, although admittedly the interaction between cardiopulmonary and arterial baroreflexes is not fully understood.

In conclusion, in 10 normal human subjects, the increase in vascular resistance was greater in the femoral artery than in the brachial artery during 60°HUT, although the decreases in femoral and brachial vascular resistance were similar to each other during LBNP. These results suggest that, during orthostatic stimulation, the vascular responses in the limbs due to the cardiopulmonary and arterial baroreflexes can be significantly modulated by local mechanisms (possibly venoarterial reflex and/or myogenic responses).

ACKNOWLEDGMENTS

We sincerely thank the volunteer subjects. We also greatly appreciate the help of Dr. Robert Timmis (English editing and critical comments).

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GRANTS

This study was supported by grants from Uehara Memorial Fundation, the Center of Excellence projects, and the Ministry of Education, Science, and Culture of Japan.

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