

Attenuated thermoregulatory sweating and cutaneous vasodilation after 14-day bed rest in humans

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Michikami, Daisaku, Atsunori Kamiya, Qi Fu, Satoshi Iwase, Tadaaki Mano, and Kenji Sunagawa. Attenuated thermoregulatory sweating and cutaneous vasodilation after 14-day bed rest in humans. *J Appl Physiol* 96: 107–114, 2004. First published August 29, 2003; 10.1152/jappphysiol.00025.2003.—We investigated the effect of head-down bed rest (HDBR) for 14 days on thermoregulatory sweating and cutaneous vasodilation in humans. Fluid intake was ad libitum during HDBR. We induced whole body heating by increasing skin temperature for 1 h with a water-perfused blanket through which hot water (42°C) was circulated. The experimental room was air-conditioned (27°C, 30–40% relative humidity). We measured skin blood flow (chest and forearm), skin temperatures (chest, upper arm, forearm, thigh, and calf), and tympanic temperature. We also measured sweat rate by the ventilated capsule method in which the skin area for measurement was drained by dry air conditioned at 27°C under similar skin temperatures in both trials. We calculated cutaneous vascular conductance (CVC) from the ratio of skin blood flow to mean blood pressure. From tympanic temperature-sweat rate and -CVC relationships, we assessed the threshold temperature and sensitivity as the slope response of variables to a given change in tympanic temperature. HDBR increased the threshold temperature for sweating by 0.31°C at the chest and 0.32°C at the forearm, whereas it reduced sensitivity by 40% at the chest and 31% at the forearm. HDBR increased the threshold temperature for cutaneous vasodilation, whereas it decreased sensitivity. HDBR reduced plasma volume by 11%, whereas it did not change plasma osmolarity. The increase in the threshold temperature for sweating correlated with that for cutaneous vasodilation. In conclusion, HDBR attenuated thermoregulatory sweating and cutaneous vasodilation by increasing the threshold temperature and decreasing sensitivity. HDBR increased the threshold temperature for sweating and cutaneous vasodilation by similar magnitudes, whereas it decreased their sensitivity by different magnitudes.

heat loss; immobilization; microgravity; spaceflight

EXPOSURE TO MICROGRAVITY AND its ground-based simulation model, 6° head-down bed rest (HDBR), increases resting core temperature (7–9, 15–17) and augments increase in core temperature during exercise (15, 16) in humans. Fortney et al. (9) reported that a 115-day spaceflight increased resting core temperature by ~0.3°C in two astronauts. One day and 12–14 days of bed rest increased resting core temperature by 0.2–0.5°C and caused an excessive increase in core temperature during submaximal exercise. Because basal or resting heat production was reported as either unchanged (16) or decreased

(20) after bed rest, the increased core temperature may be attributable to attenuation of the thermoregulatory heat-loss system. A recent study has reported that HDBR attenuated thermoregulatory cutaneous vasodilation, whereas it increased the threshold temperature and decreasing sensitivity (7, 15). However, although sweating has an important role in thermoregulatory heat loss, few studies have addressed the effect of spaceflight (9) and its simulation (8, 16) on thermoregulatory sweating. Apart from a case report of two returning astronauts (9), no studies have reported core temperature-sweating relationships, threshold temperature for onset, and the sensitivity in response to increase in core temperature after real and simulated microgravity. Therefore, it remains unclear how microgravity alters thermoregulatory sweating.

In the present study, we hypothesized that 1) HDBR increases the threshold temperature for thermoregulatory sweating, whereas it decreases its sensitivity and that 2) HDBR alters the thermoregulatory heat loss system of sweating and cutaneous vasodilation by increasing the threshold temperature, whereas it decreases sensitivity by similar magnitudes. To test our hypotheses, we investigated the effect of HDBR on thermoregulatory sweating and cutaneous vasodilation in humans. We performed 14-day HDBR in nine healthy male volunteers. Before and after HDBR, we conducted whole body heating for 1 h by using a water-perfused blanket. We investigated the thermoregulatory core temperature-sweat rate relationship by calculating the threshold temperature for the onset and the sensitivity of sweating in response to increase in core temperature.

METHODS

Subjects. Subjects were nine healthy male volunteers with the following physical characteristics: age 18–24 yr [20.2 ± 0.6 (SE) yr], height 168.2–182.1 cm (173.1 ± 0.8 cm), and weight 56.2–84.8 kg (68.2 ± 4.0 kg). Written, informed consent was obtained from each participant. The study was approved by the Committee on Human Research, Research Institute of Environmental Medicine, Nagoya University and also by the Ethical Committee of the National Space Development Agency of Japan. All subjects were evaluated as healthy by preliminary medical checkup, including physical examination, resting electrocardiogram, a panel of blood chemistry analyses, medical history, and psychological tests. None of the subjects smoked or had chronic medical problems, and all denied using recreational drugs. All subjects were physically active but were not athletes.

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HDBR. Each subject underwent 14 days of strict adherence to 6° HDBR. From 14 days before until 2 days after HDBR, all subjects lived in an air-conditioned bed rest room at a temperature of 25–26°C and relative humidity of 30–40%. During the HDBR, staff nurses continuously monitored subjects to ensure that they remained in the 6° head-down position and performed no physical exercise. Electrocardiogram and arm blood pressure were noninvasively recorded for 30 min/day during HDBR. All recordings were conducted while subjects remained in the 6° head-down position. Dietary intake was restricted to between 2,000 and 2,100 kcal/day (55% carbohydrate, 25% fat, 20% protein), including ~3,000 mg/day of sodium. Fluid intake was ad libitum, resulting in an intake of 1,100–1,600 ml/day. The photoperiod was 16 h of light and 8 h of dark, with lights on at 0700. Drinking of caffeine-containing and alcoholic beverages was strictly prohibited throughout the experiment.

Protocol. Each subject underwent experiments with whole body heating 7–14 days before and immediately after HDBR. They were prohibited from eating for at least 3 h before the each experiment. The experimental room was air conditioned at a temperature of 27°C and relative humidity of 30–40%.

In the pre-HDBR experiment, each subject lay on the bed in the horizontally supine position for at least 30 min before the experiments. We then made preheating baseline measurements of variables for 10 min. Next, we covered the entire body (except for the head, face, and forearms) with a water-perfused blanket (Blanketrol II, CSZ, Cincinnati, OH) while making preparations to measure the thermoregulatory variables. We performed whole body heating by increasing skin temperature for 1 h with the blanket, through which hot water (42°C) was circulated at a rate of ~2.0 l/min. In our preliminary experiment, we observed that this blanket heating caused reproducible increases in tympanic temperature of ~0.3°C, with a rate of ~0.005°C/min, and increases in mean skin temperature of ~3°C with a rate of ~0.05°C/min. These increases in temperatures were slightly smaller than those reported in earlier studies (6), which used hotter circulating water (47–49°C). Because some of our subjects could not tolerate 47–49°C water in our preliminary experiment, we used 42°C water for our whole body heating. We continuously measured thermoregulatory variables during the heating.

In the post-HDBR experiment, we changed the posture of each subject from 6° head down to the horizontal position by inclining the bed. The subjects did not make any other postural changes, including standing before the blanket experiment. After the baseline recording of variables, we performed whole body heating with continuous recording of these variables, as in the pre-HDBR experiment.

Measurements. We measured sweat rate ($\text{mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$) at the chest and forearm by the ventilated capsule method (Kenz-Perispiro201, Suzuken, Nagoya, Japan). We attached the capsule to the skin by double-sided tape. The skin area for measurement was drained by dry air conditioned at the same temperature as the experimental room (27°C). We measured skin blood flow ($\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ g}^{-1}$) at the chest and forearm by laser-Doppler flowmetry (model ALF 21, Advance, Tokyo, Japan). Laser-Doppler flow provides a continuous index of skin blood flow that is not influenced by muscle blood flow (19, 29). We set measurement points for skin blood flow 1 cm apart from those for sweat rate. Because the ventilated capsule method did not produce vibrations, and the area for measurement of sweat rate was so small (0.76 cm²), we believe that their close proximity did not cause the sweat measurement to confound the skin blood flow measurements. In measurements of sweat rate and skin blood flow, we put marks on the body surface to prevent mismatching of measurement points before and after HDBR.

We measured arterial blood pressure at the right fingers with a pneumatic finger cuff (Portapres, TNO Institute of Applied Physics Biomedical Instrumentation, Soesterberg, The Netherlands). We attached the Portapres finger cuffs noninvasively to two digits of the nondominant arm and inflated them alternately to prevent pain caused

by continuous air pressure load. We calculated mean blood pressure as follows

$$\text{Mean blood pressure} = \text{diastolic blood pressure} + \frac{1}{3} (\text{systolic} - \text{diastolic blood pressure})$$

We calculated cutaneous vascular conductance from the ratio of skin blood flow to mean blood pressure.

We measured tympanic temperature at the tympanic membrane using a thermistor with a precision of 0.01°C. We used tympanic temperature as an index of core temperature, despite some limitations (see *Limitations* in DISCUSSION). To ensure placement against the tympanic membrane, an audible scratching sound had to be heard by the subject when the probe was inserted. We measured skin temperature at five points (chest, upper arm, forearm, thigh, and lower leg) using thermistors (Sensor Technica, Seto, Aichi, Japan) with a precision of 0.05°C. We calculated mean skin temperature in the same manner as earlier studies (28). On the chest or the forearm, we measured skin temperature near measurement points for sweat rate and skin blood flow. We put marks on the body surface to prevent mismatching of measurement points of skin temperatures before and after HDBR.

We obtained venous blood samples from the left antecubital vein to determine the hematocrit and plasma osmolarity. Each subject lay on the bed in the horizontally supine position with left forearm extended during this procedure. We took the first blood sample 10 min before baseline measurements of thermoregulatory variables (at least 3 h after the last meal and drink) and the second sample 1 min after completion of whole body heating. Relative change in plasma volume was assessed from hematocrit values before and after HDBR (2). We measured body weight by a digital lift scale (model NSK-305, Nakagawa Seikou, Tokyo, Japan) with a precision of 0.1 kg.

Data analysis. Sweat rate, skin blood flow, arterial pressure, cutaneous vascular conductance, and core and skin temperatures were averaged for 1 min before and during heating. Sweat rate and cutaneous vascular conductance at the chest and forearm were plotted against the corresponding core temperature in each trial. We defined the threshold core temperature for sweating as the tympanic temperature when sweat rate began to progressively increase and exceeded $0.06\text{ mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$ (11, 22) and that for cutaneous vasodilation as the temperature when cutaneous vascular conductance began to progressively increase (5, 6) and exceeded $0.25\text{ ml}\cdot 100\text{ g}^{-1}\cdot\text{min}^{-1}\cdot 100\text{ mmHg}^{-1}$ above the resting level. We performed linear least squares regression analysis using the tympanic temperatures, sweat rate, and cutaneous vascular conductance above the threshold core temperature (5, 6, 11, 12, 22). We defined the sensitivity of sweating as the regression slope of sweat rate in response to given tympanic temperature (greater than threshold temperature) and that of cutaneous vasodilation as the slope of cutaneous vascular conductance in response to the temperature.

Statistical analysis. We expressed our data as means \pm SE. We evaluated the effects of the HDBR on variables by a two-way repeated-measures analysis of variance [condition (before vs. after HDBR) and protocol time]. When we found the main effect or interaction term to be significant, we made post hoc comparisons by using the Sheffé's *F* procedure. We evaluated the effects of the HDBR on the threshold temperature and sensitivity for sweating and cutaneous vasodilation by using a paired Student's *t*-test. We considered the $P < 0.05$ level of differences to be statistically significant.

RESULTS

Baseline variables in thermoneutral condition before and after HDBR. HDBR reduced plasma volume by $10.6 \pm 2.1\%$ ($P < 0.05$), whereas it did not change plasma osmolarity (from 281.7 ± 1.2 to 281.4 ± 1.1 osmol/l; $P = 0.23$). It increased the hematocrit by 6.8% (from 47.1 to 50.0%; $P < 0.0005$),

whereas it reduced body weight by $3.4 \pm 2.1\%$ (from 68.2 ± 4.0 to 63.1 ± 2.7 kg; $P < 0.001$). It increased resting tympanic temperature from 36.65 ± 0.12 to $36.98 \pm 0.10^\circ\text{C}$ (Table 1; $P < 0.05$), whereas it did not change mean and local (chest and forearm) skin temperatures. It did not change resting sweat rate at the chest or the forearm. It decreased skin blood flow at the chest and the forearm (Table 1; $P < 0.05$). It did not change mean blood pressure and as a result decreased cutaneous vascular conductance at the chest and the forearm (Table 1; $P < 0.05$). It increased heart rate from 60.3 ± 1.5 to 69.9 ± 2.0 beats/min ($P < 0.001$).

Responses of variables to whole body heating before and after HDBR (Table 1). Whole body heating increased mean and local (chest and forearm) skin temperatures by similar magnitudes before and after HDBR. HDBR did not change increases in heart rate during heating ($+8.1 \pm 1.8$ beats/min before HDBR vs. $+9.3 \pm 2.0$ beats/min after HDBR). Although whole body heating increased tympanic temperature both before and after HDBR, the increase was significantly smaller after HDBR (time \times condition interaction; $P < 0.0001$). Although whole body heating increased the sweat rate at the chest and forearm before and after HDBR, the increase was smaller after HDBR (time \times condition interaction; $P < 0.01$). Although whole body heating increased skin blood flow at the chest and forearm before and after HDBR, the increase was significantly smaller after HDBR (time \times condition interaction; $P < 0.05$). Although whole body heating increased cutaneous vascular conductance at the chest and forearm, the increase was significantly smaller after HDBR (time \times condition interaction; $P < 0.05$). Mean blood pressure remained constant during body heating before and after HDBR.

Thermoregulatory core temperature-sweating relationship before and after HDBR. Figure 1A shows response of sweat rate to whole body heating as a function of tympanic temperature in a typical subject. The figure shows that HDBR increased the threshold tympanic temperature for onset of sweating, whereas it decreased the sensitivity, assessed as increase in sweat rate in response to tympanic temperature (greater than threshold temperature). For all subjects, HDBR raised the threshold temperature for onset of sweating at the chest and the

Table 1. Core and skin temperatures (mean, chest, and forearm) at rest and during whole body heating before and after HDBR

Time	T _{core} , °C	Mean T _{sk} , °C	Chest T _{sk} , °C	Forearm T _{sk} , °C
<i>Before HDBR</i>				
Rest	36.65±0.12	34.45±0.28	35.40±0.38	34.34±0.39
15 min	36.68±0.10	36.77±0.40†	37.45±0.24†	35.79±0.28†
30 min	36.78±0.10†	37.31±0.31†	37.75±0.17†	36.46±0.23†
45 min	36.86±0.13†	37.49±0.28†	37.82±0.14†	36.64±0.29†
60 min	36.93±0.15†	37.52±0.29†	37.82±0.14†	36.80±0.23†
<i>After HDBR</i>				
Rest	36.98±0.10*	33.88±0.21	34.83±0.20	33.94±0.14
15 min	36.99±0.09*	36.83±0.28†	37.64±0.13†	35.88±0.35†
30 min	37.05±0.10*†	37.32±0.28†	38.03±0.14†	36.36±0.36†
45 min	37.10±0.09*†	37.53±0.28†	38.16±0.14†	36.61±0.33†
60 min	37.14±0.08*†	37.64±0.27†	38.19±0.11†	36.79±0.32†

Values are means \pm SE. HDBR, head-down bed rest; T_{core}, core temperature; T_{sk}; skin temperature. * $P < 0.05$ vs. before HDBR. † $P < 0.05$ vs. resting value.

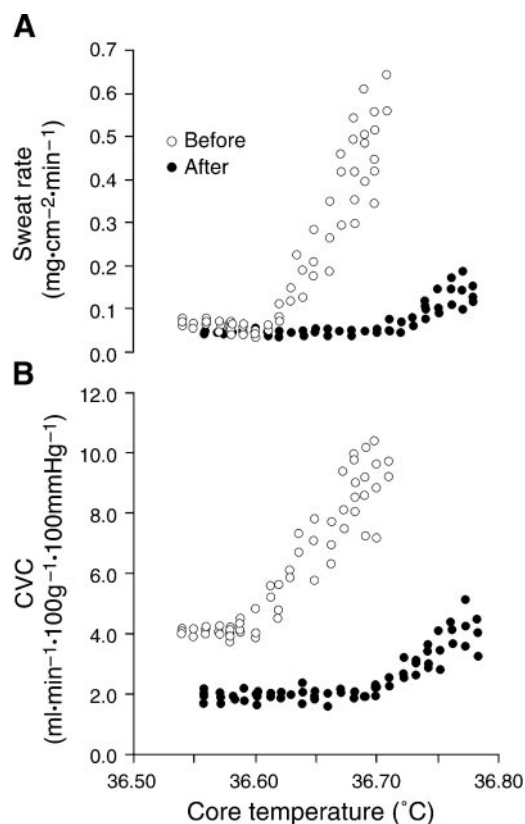


Fig. 1. Thermoregulatory sweating and cutaneous vasodilation before and after head-down bed rest (HDBR). A: sweat rate response (at the chest) to whole body heating as a function of tympanic temperature in 1 typical subject before and after HDBR. B: cutaneous vascular conductance response (at the chest) to whole body heating as a function of tympanic temperature in 1 typical subject before and after HDBR.

forearm (Fig. 2). HDBR increased the threshold temperature at the chest from 36.75 ± 0.14 to $37.05 \pm 0.09^\circ\text{C}$ ($P < 0.05$), whereas it increased that at the forearm from 36.72 ± 0.13 to $37.04 \pm 0.08^\circ\text{C}$ ($P < 0.05$; Fig. 3). HDBR decreased the sensitivity at the chest from 4.20 ± 1.15 to 2.50 ± 1.18 $\text{mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}\cdot^\circ\text{C}^{-1}$ ($P < 0.05$) and that at the forearm from 4.20 ± 1.06 to 2.92 ± 0.98 $\text{mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}\cdot^\circ\text{C}^{-1}$ ($P < 0.05$; Fig. 3).

Thermoregulatory core temperature-cutaneous vasodilation relationship before and after HDBR. Figure 1B shows response of cutaneous vascular conductance to whole body heating as a function of tympanic temperature in a typical subject. The figure shows that HDBR increased the threshold temperature for increase in cutaneous vascular conductance, whereas it decreased the sensitivity, assessed as increase in cutaneous vascular conductance in response to tympanic temperature (greater than threshold temperature) at the chest and the forearm. For all subjects, HDBR raised the threshold temperature for increase in cutaneous vascular conductance both at the chest and the forearm (Fig. 2). HDBR increased the threshold temperature at the chest from 36.74 ± 0.10 to $37.01 \pm 0.09^\circ\text{C}$ ($P < 0.05$) that at the forearm from 36.72 ± 0.13 to $37.00 \pm 0.08^\circ\text{C}$ ($P < 0.05$; Fig. 3). HDBR decreased the sensitivity at the chest from 68.5 ± 10.7 to 43.2 ± 7.9 $\text{ml}\cdot\text{min}^{-1}\cdot 100$ $\text{g}^{-1}\cdot 100$ $\text{mmHg}^{-1}\cdot^\circ\text{C}^{-1}$ ($P < 0.05$) and that at the forearm

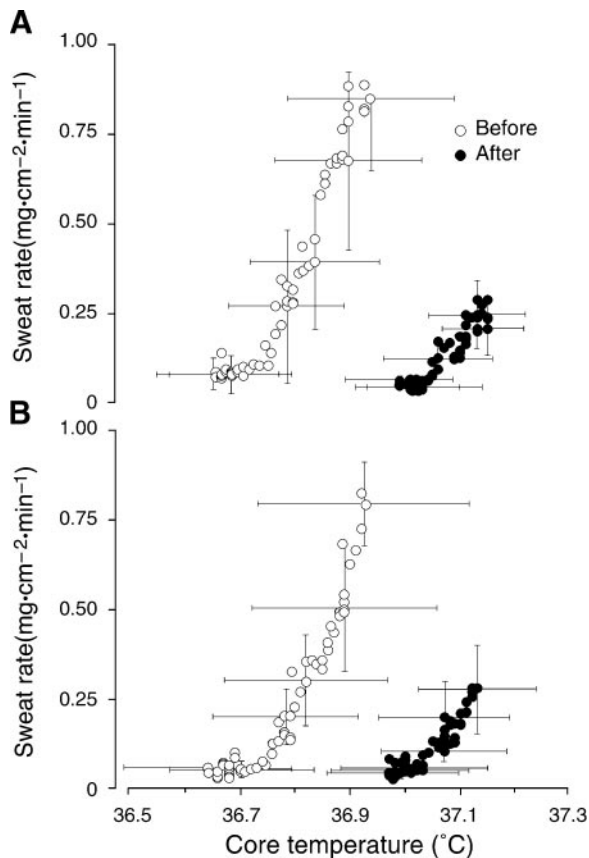


Fig. 2. Core temperature-sweat rate relationship at the chest (A) and forearm (B) during whole body heating before and after HDBR. Values are means \pm SE.

from 73.2 ± 11.8 to 39.1 ± 8.1 $\text{ml}\cdot\text{min}^{-1}\cdot 100$ $\text{g}^{-1}\cdot 100$ $\text{mmHg}^{-1}\cdot\text{C}^{-1}$ ($P < 0.05$; Fig. 3).

Relationship between changes in sweating and cutaneous vasodilation after HDBR (Fig. 4). HDBR-induced increase in the threshold temperature for sweating correlated with that for cutaneous vasodilation both at the chest ($r = 0.87$, $P < 0.005$) and forearm ($r = 0.99$, $P < 0.0001$; Fig. 4A). HDBR-induced decrease in the sensitivity of sweating did not correlate with that for cutaneous vasodilation either at the chest ($r = -0.63$, $P = 0.067$) or forearm ($r = -0.36$, $P = 0.46$; Fig. 4B).

Relationship between changes in thermoregulation and increase in resting core temperature after HDBR (Table 3). HDBR-induced increase in the threshold temperature for sweating correlated with the increase in resting tympanic temperature both at the chest ($r = 0.98$, $P < 0.0001$) and forearm ($r = 0.99$, $P < 0.0001$). HDBR-induced decrease in the sensitivity of sweating did not correlate with resting tympanic temperature at either the chest ($r = -0.089$, $P = 0.84$) or forearm ($r = -0.50$, $P = 0.27$).

HDBR-induced increase in the threshold temperature for cutaneous vasodilation correlated with increase in resting tympanic temperature both at the chest ($r = 0.89$, $P < 0.0001$) and forearm ($r = 0.98$, $P < 0.0001$). HDBR-induced decrease in the sensitivity of cutaneous vasodilation did not correlate with increase in resting tympanic temperature at either the chest ($r = -0.25$, $P = 0.52$) or forearm ($r = 0.55$, $P = 0.13$).

Relationship between changes in thermoregulation and those in plasma volume and osmolarity after HDBR (Table 4).

There was no correlation between reduction of plasma volume after HDBR and threshold temperatures for sweating or cutaneous vasodilation, nor with decrease in sensitivity at the chest or forearm. There was no correlation between change in plasma osmolarity after HDBR and threshold temperatures for sweating or cutaneous vasodilation, nor with decrease in sensitivity at the chest or forearm.

DISCUSSION

We investigated changes in thermoregulatory sweating after HDBR in humans. The first major new finding of the present study was that threshold core temperature for sweating onset was elevated by 0.31°C at the chest and 0.32°C at the forearm after 14-day HDBR and that sweating sensitivity was reduced by 40% at the chest and 31% at the forearm after HDBR. These findings support our first hypothesis that HDBR increases the threshold temperature for thermoregulatory sweating, whereas it decreases its sensitivity. They indicate that HDBR attenuated the thermoregulatory heat loss response of sweating. After HDBR, sweating is not activated until core temperature is elevated by an additional 0.3°C . Even after activation, sweating develops with less sensitivity in response to increase in core temperature.

We also observed that the threshold temperature for cutaneous vasodilation was elevated by 0.27°C at the chest and

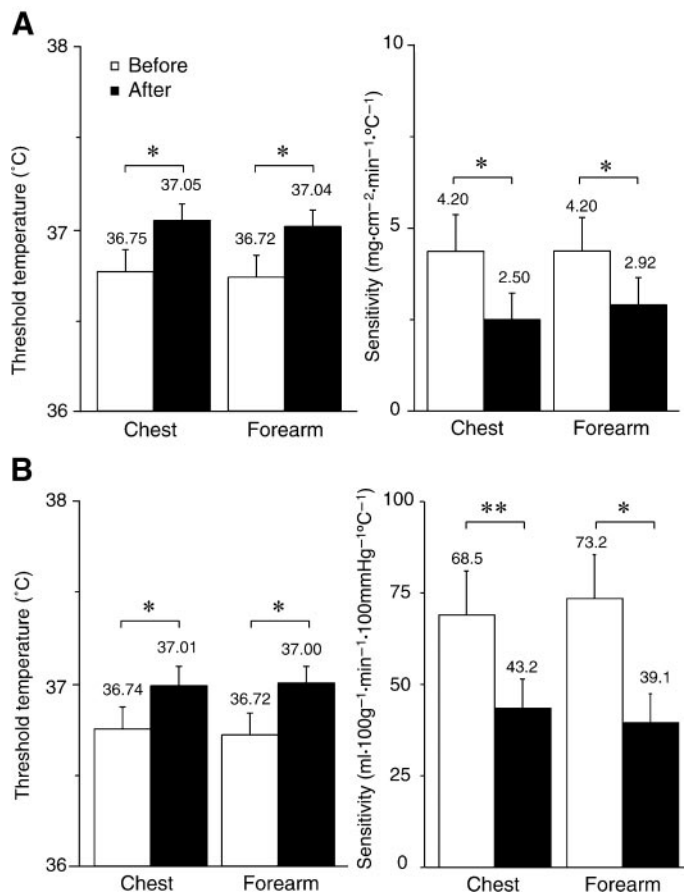


Fig. 3. Change in threshold temperature (left) and sensitivity (right) during whole body heating before and after HDBR. A: sweat rate. B: cutaneous vascular conductance. Values are means \pm SE. * $P < 0.05$. ** $P < 0.01$.

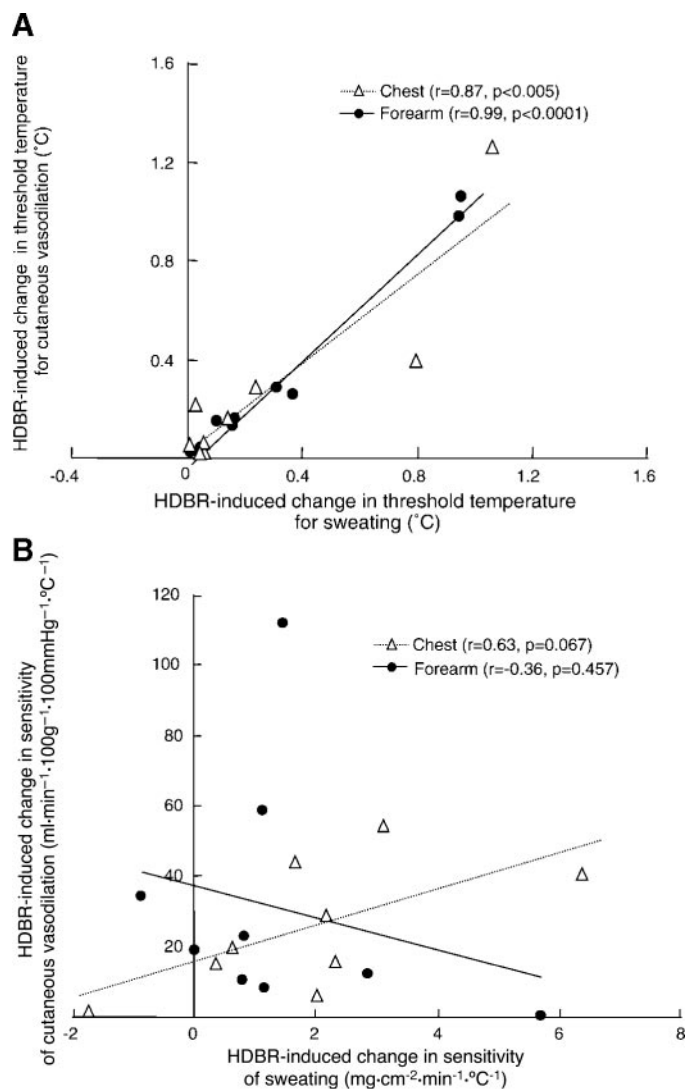


Fig. 4. Relationship between changes in threshold temperature for sweating and for cutaneous vasodilation (A) and between changes in sensitivity of sweating and of cutaneous vasodilation (B) after HDBR.

Table 3. Relationship between changes in thermoregulation and increase in resting core temperature after HDBR

	vs. Resting Core Temperature
Sweat rate	
Threshold temperature at the chest	$r=0.98$ ($P<0.0001$)
Threshold temperature at the forearm	$r=0.99$ ($P<0.0001$)
Sensitivity at the chest	$r=-0.09$ ($P=0.84$)
Sensitivity at the forearm	$r=0.50$ ($P=0.27$)
Cutaneous vascular conductance	
Threshold temperature at the chest	$r=0.89$ ($P<0.0001$)
Threshold temperature at the forearm	$r=0.98$ ($P<0.0001$)
Sensitivity at the chest	$r=-0.25$ ($P=0.52$)
Sensitivity at the forearm	$r=0.55$ ($P=0.13$)

0.28°C at the forearm and that sensitivity of cutaneous vasodilation was 40% at the chest and 44% at the forearm lower after 14-day HDBR. To our knowledge, the present study is the first to investigate the relationship between changes in sweating and cutaneous vasodilation after HDBR (Fig. 4). The second major new finding of the present study was that the increase in threshold temperature for cutaneous vasodilation after HDBR correlated with that for sweating. The data partially support our second hypothesis (see the Introduction) as to the threshold temperature. They demonstrate that HDBR increased the threshold temperature of both sweating and cutaneous vasodilation by similar magnitudes.

The elevation of threshold temperature for both thermoregulatory heat loss systems seen after HDBR is interesting, given their relation with the increase in resting core temperature after HDBR (Table 3). We found that individual increases in threshold temperature for sweating and cutaneous vasodilation after HDBR correlated with an individual increase in resting core temperature. We observed this correlation at both the chest and forearm. Accordingly, the increases in threshold temperature for thermoregulatory heat loss sweating and cutaneous vasodilation may contribute to increase resting core temperature after HDBR. These findings suggest a set point change in thermoregulation after HDBR.

In contrast to the general increase in threshold temperature, the magnitude of individual decrease in the sensitivity of the

Table 2. Sweat rate, cutaneous vascular conductance, and skin blood flow at rest and during whole body heating before and after HDBR

Time	Sweat Rate, $\text{mg}\cdot\text{cm}^{-2}\cdot\text{min}^{-1}$		CVC, $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ g}^{-1}\cdot 100\text{ mmHg}^{-1}\cdot\text{C}^{-1}$		SkBF, $\text{ml}\cdot\text{min}^{-1}\cdot 100\text{ g}^{-1}$		MBP, mmHg
	Chest	Forearm	Chest	Forearm	Chest	Forearm	
<i>Before HDBR</i>							
Rest	0.08 ± 0.02	0.07 ± 0.02	4.02 ± 0.29	4.46 ± 0.39	3.48 ± 0.41	3.81 ± 0.41	87.2 ± 2.49
15 min	0.08 ± 0.07	0.08 ± 0.06	4.77 ± 0.68	6.28 ± 0.62	4.23 ± 0.74	5.44 ± 0.74	85.2 ± 2.45
30 min	$0.38\pm 0.12\ddagger$	$0.22\pm 0.10\ddagger$	6.88 ± 0.98	$9.45\pm 0.97\ddagger$	$7.39\pm 1.19\ddagger$	$8.35\pm 1.19\ddagger$	87.4 ± 3.41
45 min	$0.59\pm 0.18\ddagger$	$0.52\pm 0.22\ddagger$	$9.87\pm 1.60\ddagger$	$12.06\pm 1.50\ddagger$	$8.03\pm 1.26\ddagger$	$11.20\pm 1.26\ddagger$	88.5 ± 4.57
60 min	$0.94\pm 0.43\ddagger$	$0.84\pm 0.35\ddagger$	$11.40\pm 2.40\ddagger$	$12.68\pm 2.80\ddagger$	$9.68\pm 3.73\ddagger$	$10.71\pm 3.73\ddagger$	86.1 ± 3.73
<i>After HDBR</i>							
Rest	0.06 ± 0.02	0.05 ± 0.02	$2.95\pm 0.24^*$	$3.03\pm 0.23^*$	$2.52\pm 0.34^*$	$2.62\pm 0.34^*$	90.0 ± 2.12
15 min	0.06 ± 0.03	0.05 ± 0.03	$3.45\pm 0.35^*$	$3.12\pm 0.32^*$	$2.92\pm 0.37^*$	$2.80\pm 0.37^*$	89.9 ± 2.66
30 min	$0.16\pm 0.04^*$	$0.08\pm 0.04^*$	$4.51\pm 0.40^*$	$3.87\pm 0.37^*$	$3.73\pm 0.46^*$	$3.47\pm 0.46^*$	89.6 ± 3.30
45 min	$0.21\pm 0.06^*\ddagger$	$0.14\pm 0.06^*\ddagger$	$4.81\pm 0.56^*$	$5.20\pm 0.58^*\ddagger$	$4.35\pm 0.54^*\ddagger$	$4.68\pm 0.45^*\ddagger$	93.3 ± 2.88
60 min	$0.29\pm 0.12^*\ddagger$	$0.31\pm 0.12^*\ddagger$	$5.69\pm 0.54^*\ddagger$	$5.78\pm 0.56^*\ddagger$	$5.03\pm 0.46^*\ddagger$	$4.83\pm 0.54^*\ddagger$	89.6 ± 5.40

Value are means \pm SE. CVC, cutaneous vascular conductance; SkBF, skin blood flow; MBP, mean blood pressure. * $P < 0.05$ vs. before HDBR. $\ddagger P < 0.05$ vs. resting value.

Table 4. Relationship between changes in thermoregulation and those in plasma volume and plasma osmolarity after HDBR

	vs. Plasma Volume	vs. Plasma Osmolarity
Sweat rate		
Threshold temperature at the chest	$r = -0.23$ ($P = 0.64$)	$r = -0.25$ ($P = 0.54$)
Threshold temperature at the forearm	$r = -0.18$ ($P = 0.72$)	$r = -0.25$ ($P = 0.57$)
Sensitivity at the chest	$r = 0.22$ ($P = 0.58$)	$r = 0.26$ ($P = 0.52$)
Sensitivity at the forearm	$r = -0.40$ ($P = 0.32$)	$r = 0.21$ ($P = 0.63$)
Cutaneous vascular conductance		
Threshold temperature at the chest	$r = -0.02$ ($P = 0.96$)	$r = -0.06$ ($P = 0.89$)
Threshold temperature at the forearm	$r = -0.18$ ($P = 0.70$)	$r = 0.01$ ($P = 0.99$)
Sensitivity at the chest	$r = 0.42$ ($P = 0.29$)	$r = 0.54$ ($P = 0.14$)
Sensitivity at the forearm	$r = 0.11$ ($P = 0.78$)	$r = -0.24$ ($P = 0.54$)

thermoregulatory heat loss system after HDBR differed between sweating and cutaneous vasodilation. We observed that the HDBR-induced decrease in the sensitivity of sweating did not correlate with that of cutaneous vasodilation at the chest or forearm. The data did not support our second hypothesis (see the Introduction). Moreover, none of the decreases in sensitivity after HDBR for sweating and cutaneous vasodilation correlated with the increase in resting core temperature. This suggests that HDBR-induced change in the sensitivity of thermoregulatory heat loss system contributes little to the increased resting core temperature after HDBR.

Few studies have addressed thermoregulatory cutaneous vasodilation and sweating after spaceflight and bed rest. Although studies by Greenleaf et al. (15) and Ertl et al. (8) examined changes in sweating, skin blood flow, and core temperature during exercise, neither of them investigated responses of sweating and cutaneous vasodilation as a function of core temperature. A preliminary report by Fortney et al. (9) showed that spaceflight (Mir-18 mission) reduced the sensitivities of sweating and cutaneous vasodilation in response to increase in core temperature but did not change threshold temperatures. However, because the number of subjects was only two, the study did not perform statistical analysis, and no conclusions could be drawn. Indeed, spaceflight obviously shifted the threshold temperature for sweating to 0.2°C higher level in one subject. In the present study, we expanded the preliminary report by using HDBR as simulation model of spaceflight, with a sufficient number of subjects ($n = 9$) for statistical analysis. We demonstrated that HDBR increased the threshold temperatures for sweating and cutaneous vasodilation by ~0.3°C.

Our findings of the attenuated thermoregulatory heat loss sweating and cutaneous vasodilation after HDBR may not contradict our observation that the increase in core temperature during whole body heating was less after HDBR for the following reason. In the thermoneutral condition, maintenance of core temperature depends on a balance between body heat production and heat loss. Although we could not provide quantitative data about heat production, the basal or resting

heat production was reported to be either unchanged (16) or decreased (20) after bed rest. We therefore postulate that the attenuated thermoregulatory heat loss system, particularly increased threshold temperature, may contribute to the increased resting core temperature after HDBR. In contrast to the thermoneutral condition, maintenance of core temperature during whole body heating is affected significantly by heat inflow to the body. Under mild thermal stress, thermoregulatory vasoconstriction is known to prevent excessive increase in core temperature by reducing cutaneous heat transfer (21). Because HDBR reduced cutaneous blood flow by ~30% (Table 1), the heat inflow to the body from the blanket would be less after HDBR. Indeed, Greenleaf and Reese (16) reported that HDBR decreased skin heat conductance. We speculate that the decreased heat inflow might override the attenuated thermoregulatory heat loss sweating and cutaneous vasodilation, resulting in a smaller increase in core temperature during whole body heating.

Because the attenuated thermoregulatory heat loss system after HDBR is presumably caused by complex mechanisms, we cannot determine the mechanism conclusively. Thus we propose several possibilities. The first possibility is HDBR-induced dehydration. In both sweating (11, 22, 31, 33) and cutaneous vasodilation (10, 24), dehydration is known to increase the threshold temperature, whereas it decreases the sensitivity in a proportionate manner. Because in the present study the magnitude of plasma volume loss after HDBR did not correlate with any changes in the threshold temperature or in sensitivity after HDBR (Table 4), loss of third-space (interstitial) fluid volume rather than plasma volume may attenuate the thermoregulatory heat loss system. We consider that the attenuated thermoregulatory heat loss may not be a simple consequence of HDBR-induced dehydration. The second possibility is change in plasma osmolarity. Plasma hyperosmolarity is known to increase the threshold temperature for sweating (12, 30, 32, 35) and cutaneous vasodilation (10). However, as in earlier studies (7), HDBR did not change plasma osmolarity in the present study.

The third possibility is heat deacclimatization. Experimental 10-day heat acclimatization to hot room air (46°C), with and without submaximal exercise, is known to decrease the threshold temperature for sweating (1, 34) and for cutaneous vasodilation (1). Because HDBR might heat-deacclimatize subjects to some extent, it could have an opposite physiological effect on the threshold temperature to heat acclimatization. Unfortunately, we did not address quantitative evaluation of heat deacclimatization with HDBR. Because the subjects lived in an air-conditioned room at a temperature of 25–26°C and relative humidity of 30–40% from 7 days before and throughout HDBR, they had not been exposed to heat strain before HDBR. In addition, because heat acclimatization is known to have little influence on the sensitivity of thermoregulatory heat loss responses (21), heat deacclimatization with HDBR could not explain the reduced sensitivity seen after HDBR.

The fourth possibility is reduction of aerobic fitness. An increase in aerobic fitness induced by exercise training has been associated with an increase in sensitivity for sweating and cutaneous vasodilation (21, 36). Because HDBR is known to decrease aerobic fitness, it could have an opposite physiological effect on the sensitivity to exercise training. We did not investigate aerobic fitness, because in our preliminary study we

found that a decrease in aerobic fitness with HDBR did not correlate with increase in resting core temperature (data not shown). Other studies have reported that aerobic fitness has little influence on thermoregulatory heat loss responses (18, 37), particularly sensitivity. Moreover, several studies have reported that improved thermoregulatory function after exercise training correlated strongly with increased plasma volume but poorly with increased aerobic fitness (13, 27, 37).

The fifth possibility is a change in central processing. A shift of threshold temperature is often interpreted as indicative of a central nervous system change in the thermoregulatory effector signal (23, 25). We found that the individual increase in the threshold temperature for sweating after HDBR correlated with that for cutaneous vasodilation. The increase might indicate a change in the set point of thermoregulation in the central nervous system after HDBR.

Additionally, there are several possible mechanisms that could explain the attenuated thermoregulatory control of cutaneous vasodilation found in the present study. It is possible that HDBR changes neurovascular control. Sympathetic vasoconstrictor control of cutaneous circulation may be enhanced, whereas sympathetic active vasodilator control could be inhibited, after HDBR. It is also possible that HDBR changes the structure of cutaneous blood vessels. If the maximal ability to dilate blood vessels were diminished by HDBR, this could explain the decreased sensitivity seen after HDBR.

Limitations. The present study has several limitations. First, although we tried to use the same locations for the laser-Doppler flowmetry probes before and after HDBR, the placement of the probes was slightly different after HDBR. If the probes were placed on a site with slightly fewer blood vessels, the responsiveness could have been affected. However, we believe that this had little effect on our data because we observed the increase in the threshold temperature and the decrease in the sensitivity for cutaneous vasodilation after HDBR in all subjects, both at the chest and forearm. Second, the present study did not have control group that was sedentary and confined but not subjected to HDBR. Although HDBR has been established as a ground-based simulation model of microgravity in humans, it could have confounding effects, including inactivity and heat deacclimatization. Although a few studies have employed this kind of control group, we could not afford an additional control group because of financial limitations. Third, although we used tympanic temperature as an index of core temperature, tympanic temperature cannot provide an accurate brain temperature. Some earlier studies (3, 4, 29) showed that tympanic temperature is comparable to esophageal and brain temperatures and could reflect core temperature. However, tympanic temperature is biased by face skin temperature.

In conclusion, 14-day HDBR attenuated thermoregulatory heat loss sweating and cutaneous vasodilation with increases in the threshold temperature of $\sim 0.3^{\circ}\text{C}$ and decreases in sensitivity of 30–40%. The HDBR increased the threshold temperature of both thermoregulatory heat loss sweating and cutaneous vasodilation by similar magnitudes, whereas it decreased their sensitivity by different magnitudes.

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