Cardiovascular responses to upright tilt in man during acute exposure to 3 atm abs air

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Sagawa S, Miki K, Tajima F, Shiraki K. Cardiovascular responses to upright tilt in man during acute exposure to 3 atm abs air. Undersea Biomed Res 1992; 19(2):97–106.—To examine the effect of acute hyperbaric exposure on cardiovascular response to orthostasis, a passive 70° head-up tilt (HUT) test was performed for 15 min in a simulated compressed-air hyperbaric environment of 3 atm abs at ambient temperature of 31°C (thermoneutral) on 8 male subjects. Heart rate (HR), blood pressure, cardiac output (CO) by impedance cardiography, forearm blood flow (FBF) by the occlusion plethysmography, and laser-Doppler skin blood flow (BF_{10}) on the thigh were measured for 15 min before, during, and after HUT. Esophageal temperature and HR data were recorded continuously. An identical test was performed in a 29°C (thermoneutral) normal atmospheric condition. None of the subjects showed signs of syncope during HUT in either environment. Baseline HR was significantly lower (P < 0.05) at 3 atm abs, and the increase in HR (ΔHR) during HUT was of the same magnitude (15 beats/min) at both atmospheric pressures. The reduction of systolic blood pressure (ΔSBP) was identical in both environments. Thus, the chronotropic response to HUT (ΔHR/ΔSBP) was the same. A marked reduction in CO (P < 0.05) was attributed to a reduction of stroke volume during HUT, and the reduction was greater (P < 0.05) at 3 atm abs. There were no pressure-dependent changes during HUT in FBF, forearm vascular resistance, and BF_{10}, except for a greater increase (P < 0.05) in total peripheral resistance at 3 atm abs. These observations suggest that orthostatic tolerance was maintained in the presence of lower CO at 3 atm abs, probably by a greater vasoconstrictor response in the splanchnic areas. We conclude that the substantial bradycardia which occurred at 3 atm abs did not interfere with a normal response to orthostasis in humans because of a peripheral vasoconstriction caused by the elevated oxygen pressure and an enhanced increase in total peripheral resistance which occurred during HUT in 3 atm abs.

Bradydcardia during exposure to high ambient pressure (hyperbaric bradycardia) has been observed in humans under resting conditions (1–3) and during exercise (4, 5). Although the mechanisms involved are unknown, it has been suggested that both an elevated partial pressure of oxygen (Po2), and hyperbaria per se are responsi-
ble (6). This bradycardia is probably the result of a parasympathetic vagal dominance over the sympathetic nervous system in control of heart rate. Since the bradycardia observed during early stages of hyperbaric exposure is restored to normal after 24 h (7), hyperbaric bradycardia seems to be a transient response. In addition to hyperbaric bradycardia, elevation in \( \text{PO}_2 \) also induces a vasoconstrictor response in most tissue (8), which may be due to an increase in sympathetic nerve activity or a direct effect of the high oxygen tension in the blood on the resistance vessels. Thus, elevated \( \text{PO}_2 \) has an effect on the heart and on vascular smooth muscle, although the mechanisms responsible for these effects may not be the same.

The orthostatic tolerance test, where unloading of arterial and cardiopulmonary baroreceptors results in an increase in sympathetic outflow, tachycardia, and vasoconstrictor response in humans (9), is useful to determine whether cardiovascular responsiveness is altered by hyperbaria. A reduction in tolerance to orthostasis has been observed during chronic exposure (7 days) to high pressure (10), but no bradycardia was observed before the orthostatic tolerance test.

Does hyperbaric bradycardia, which occurs with acute high pressure exposure, attenuate orthostatic tolerance or does the vasoconstrictor response to an elevated \( \text{PO}_2 \) have an additive effect with the vasoconstriction during orthostasis to offset the bradycardia? The answer to this question is of prime importance to further delineate the interaction between the sympathetic and parasympathetic nervous systems and \( \text{PO}_2 \) in high pressure, particularly since the response to both orthostasis and elevated \( \text{PO}_2 \) is vasoconstriction, which should help compensate for a preexisting bradycardia.

The present study was designed to test orthostatic tolerance during acute exposure to a compressed-air high pressure environment of 20 m (3 atm abs \( \text{PO}_2 = 477 \text{ mmHg} \)). The purpose of the study is therefore to examine the interaction between the cardioacceleration of orthostasis and hyperbaric bradycardia, and to assess whether the vasoconstrictor response is modified by orthostasis and elevated \( \text{PO}_2 \).

**MATERIALS AND METHODS**

**Subjects**

Eight healthy male subjects (27 ± 3 yr, 173 ± 3 cm height, 68 ± 2 kg body weight) volunteered for this study. None of the subjects engaged in athletic exercise. Each subject signed a consent form after receiving a detailed description of the procedure and a comprehensive medical examination.

**Experimental protocol**

Each subject arrived at the laboratory at 0830 h, dressed in cotton underwear, and entered a temperature-regulated pressure chamber \([\text{Ta} = 29^\circ\text{C}, 60\% \text{ relative humidity (RH)}]\). After the subject lay supine on the tilt table located in the chamber, he was outfitted with skin thermocouples (copper-constantan), an esophageal temperature probe, heat flux transducers, ECG electrodes, twin tape-on mylar electrodes for measuring cardiac output (CO), a mercury-insilastic Whitney strain gauge for forearm blood flow (FFB), a laser-Doppler flow probe for measurement of skin blood flow (BF\(_{LD}\)) on the thigh, and a blood pressure cuff on the upper arm. This preparation
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was completed within 30 min, and the subject maintained a relaxed position on the tilt table for an additional 30 min before any measurements (60-min rest period). After this rest period all measurements were performed for a 15-min control period [pre-head-up tilt (HUT)]. Both arms rested at heart level on shelves fastened to the tilt table. When the position was changed, a foot-board at the base of the tilt table and straps on the arms, chest, and thighs supported the subject; the straps did not impede the circulation. Heart rate (HR), BF\textsubscript{LD}, skin (T\textsubscript{s}), and esophageal (T\textsubscript{e}) temperatures were monitored continuously throughout the experimental period. Blood pressure and CO were measured every 3 min during the control period and every 2 min during the tilting and recovery periods. FBF was measured every minute throughout the experiment. After the pre-HUT period, the tilt table was raised to 70° within 3 s, maintained in the HUT position for 15 min, and then returned to the horizontal for 15 min. Care was taken to ensure that the subject was completely relaxed during HUT, and a physician was always in attendance during the test. The ECG was monitored continuously, displayed on an oscilloscope, and recorded on a San-ei Recti-Horiz-8K eight-channel polygraph.

On completion of the tilt test at normal atmosphere (1 atm abs), each subject, while relaxing in the chamber, was compressed to 3 atm abs (20 m seawater depth); the chamber was pressurized with air at a rate of 150 mmHg/min. Chamber temperature and RH were maintained at 31°C and 60%, respectively, except for unavoidable transient heating during the compression. This environment was thermoneutral at this depth and was equivalent to that at T\textsubscript{s} = 29°C, RH 60% at normal atmospheric pressure with respect to heat exchange between human and the environment (11). After reaching the designated pressure and ambient conditions, the subject was allowed to relax for about 30 min before beginning the same experimental procedures as at 1 atm abs. Usually, temperature and humidity stabilized in 30 min after reaching the designated pressure, so the subject had been exposed to pressure for 60 min before the start of the HUT test.

Measurements

Blood pressure was determined with a pressure transducer (Validyne, DP-15) connected to a conventional pressure cuff applied on the left arm of the subject at heart level. Systolic (SBP) and diastolic (DBP) blood pressures were read from the pressure wave recorded on a chart. Mean arterial blood pressure (MAP) was calculated as one third of pulse pressure plus DBP. CO was estimated by impedance cardiography (AI-601G, Nihonkohden, Tokyo, Japan), using the standard four-band electrode arrangement (12). This method has been shown to be useful for measurements of CO changes in postural stress (13). A Whitney mercury-in-silastic circumference strain gauge was placed on the right midforearm for measurement of FBF, and a cuff was secured on the upper arm; venous congestive pressure was 40 mmHg. In the present experiment, values of FBF included blood flow to the hand because we did not occlude the wrist during the measurement. Total peripheral resistance (TPR) was calculated by dividing MAP in mmHg by CO in liters per minute. Forearm vascular resistance (FVR) was calculated as MAP/FBF. BF\textsubscript{LD} was monitored continuously on the thigh with a laser-Doppler flow meter (TSI, BPM-403, St. Paul, MN); the glass-fiber sensor probe was placed midpoint on the flexor side of the right thigh and maintained in exactly the same position throughout the study. The laser-Doppler
flowmetry measures mainly the average blood flow in the outermost cutaneous tissue (0.6–1.5 mm depth); the principle of the device has been documented elsewhere (14). Although BF_LD provides a good indicator for the response of skin blood flow (15, 16), the flow meter did not measure the absolute value of the skin blood flow. Therefore, changes in skin blood flow were estimated from percent changes in the voltage output from the pre-HUT level at both environments.

Skin temperatures were measured with seven copper-constantan thermocouples on the forehead, chest, forearm, hand, thigh, calf, and foot. The mean Tsk was calculated using the weighting factors of Hardy and DuBois (17). Esophageal temperature was measured with a polyethylene-sealed thermocouple (0.6 mm diameter) positioned 38 cm from the incisors at the level of the atrium, and the position was confirmed by x-ray. For measurement of convective heat exchange at the skin surface, a laboratory-calibrated heat flux transducer (Thermonetics, HA-13-18-10P) was placed near each temperature thermocouple and secured with surgical tape (18). Total convective heat loss from the skin was calculated as regional heat exchange of the seven sites times respective regional area. For the regional area the same weighting factor as that for Tsk (17) was applied.

Body temperatures, BF_LD, and HR were monitored continuously, stored every 15 s on a data logger (7V14, San-ei Sokki, Tokyo), and analyzed with a computer (NEC, PC-9801VX, Tokyo). All recordings were made outside the chamber.

Statistical analysis

Measurements during tilting at 3 atm abs were compared with corresponding supine data at 1 atm abs using a two-way analysis of variance; further significance was tested by multiple comparisons between experimental groups utilizing Fisher’s least significant difference test (19). Data are expressed as means ± SE, with a value of \( P < 0.05 \) considered significant.

RESULTS

The major finding in the present study was that none of the subjects showed signs of syncope during HUT in either environment. However, there were some characteristic differences in the cardiovascular response to HUT.

Circulatory changes

Arterial blood pressure

The average baseline blood pressures were identical at both atmospheric pressures. SBP significantly decreased \( (P < 0.05) \) at the beginning of the tilt in both environments and remained at this depressed level throughout HUT (Fig. 1). DBP was increased at the 6–10 min of HUT at 1 atm abs \( (P < 0.05) \), but at 3 atm abs it was constant throughout the experiment. No significant change in MAP was observed in either environment. Restoration of blood pressure was prompt in both environments.
Cardiac changes

The average baseline HR was significantly lower ($P < 0.05$) at 3 atm abs than at 1 atm abs (Fig. 1). A sustained increase in HR (15 beats/min) was observed during HUT in both environments. At both pressures, baseline stroke volume (SV) and the significant reduction ($P < 0.05$) during HUT were the same. Accordingly, CO was significantly lower ($P < 0.05$) during HUT at 3 atm abs (Fig. 1). HR, SV, and CO returned to baseline levels within 1 min of the recovery period. The ratio of HR change to SBP change ($\Delta HR/\Delta SBP$) for use as an estimation of the chronotropic response (20, 21) was identical in both environments (Table 1).

Blood flow changes

A significantly lower ($P < 0.05$) baseline FBF (7.1 ± 1.0 ml ⋅ 100 ml$^{-1}$ ⋅ min$^{-1}$ at 1 atm abs vs. 5.3 ± 0.6 ml ⋅ 100 ml$^{-1}$ ⋅ min$^{-1}$ at 3 atm abs) was observed at 3 atm abs (Fig. 2), indicating a substantial vasoconstriction in the hyperbaric environment.

![Fig. 1. Mean cardiovascular responses to HUT at normal atmospheric pressure (1 atm abs, solid line) and 3 atm abs (dashed line). Asterisks = $P < 0.05$ vs. pretilt supine value; daggers = $P < 0.05$ vs. 1 atm abs value; (#) = $P < 0.05$ vs. 1 atm abs value throughout the period.](image_url)
### TABLE 1
**VASCULAR RESPONSES TO HEAD-UP TILT AT 1 AND 3 ATM ABS**

<table>
<thead>
<tr>
<th></th>
<th>Pre-HUT</th>
<th>HUT</th>
<th>$\Delta$</th>
<th>Post-HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FVR, mmHg · ml⁻¹ · 100 ml⁻¹ · min⁻¹</strong></td>
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<tr>
<td>1 atm abs</td>
<td>11.2 ± 1.1</td>
<td>20.3 ± 2.8$^b$</td>
<td>9.1 ± 2.6</td>
<td>9.6 ± 0.9</td>
</tr>
<tr>
<td>3 atm abs</td>
<td>15.1 ± 1.6</td>
<td>23.0 ± 2.4$^b$</td>
<td>7.9 ± 2.3</td>
<td>12.0 ± 1.4</td>
</tr>
<tr>
<td><strong>TPR mmHg · liter⁻¹ · min⁻¹</strong></td>
<td></td>
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<tr>
<td>1 atm abs</td>
<td>12.1 ± 0.7</td>
<td>16.9 ± 1.0$^b$</td>
<td>4.8 ± 0.8</td>
<td>13.2 ± 0.7</td>
</tr>
<tr>
<td>3 atm abs</td>
<td>14.1 ± 1.0</td>
<td>20.6 ± 1.4$^{b,c}$</td>
<td>6.6 ± 1.2$^c$</td>
<td>14.0 ± 0.7</td>
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<tr>
<td><strong>ΔHR/ΔSBP</strong></td>
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<td></td>
</tr>
<tr>
<td>1 atm abs</td>
<td>–</td>
<td>2.04 ± 0.55</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3 atm abs</td>
<td>–</td>
<td>2.13 ± 0.51</td>
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<td>–</td>
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</tbody>
</table>

$^a$Values are means ± se for average values during respective experimental period. $\Delta$HR/ΔSBP, unit change in HR from pretilt per unit change in SBP; $\Delta$, change from pre-HUT value.

$^bP < 0.05$ vs. pretilt supine values; $^cP < 0.05$ vs. 1 atm abs values.

HUT decreased FBF significantly ($P < 0.05$) in both environments. The baseline $\text{BF}_{\text{LD}}$ was less at 3 atm abs compared with 1 atm abs (319 ± 48 mV at 1 atm abs vs. 234 ± 49 mV at 3 atm abs, $P < 0.05$); however, the HUT-induced reduction (percent change from the pre-HUT value) was identical in both environments (Fig. 2). Both FBF and $\text{BF}_{\text{LD}}$ returned to baseline levels within 1 min of the recovery period.

The average baseline FVR, its increase during HUT ($P < 0.05$), and its swift restoration during recovery were the same in both environments (Fig. 2 and Table 1). Baseline TPR tended to be higher in the 3 atm abs environment compared with the 1 atm abs, probably because of the relative vasoconstriction of the skin as shown by decreased FBF and $\text{BF}_{\text{LD}}$. During HUT there was a significant increase ($P < 0.05$) in TPR at both 1 and 3 atm abs (Fig. 2 and Table 1). However, the increase in TPR was significantly enhanced ($P < 0.05$) at 3 atm abs compared with 1 atm abs. This augmented increase in TPR at 3 atm abs is probably not due to an enhanced vasoconstriction in the periphery because the changes in FBF, FVR, and $\text{BF}_{\text{LD}}$ were similar in the two atmospheres (Fig. 2). Thus, the increased TPR during HUT must be the result of a vasoconstriction in another vascular bed.

**Body temperature and convective heat loss**

The baseline level of $T_{es}$ and $T_{sk}$ was identical in the two environments. There was no HUT-induced change in $T_{sk}$ (data not shown). There was a trend for $T_{es}$ to increase during HUT in both environments (Fig. 2), but the change was significant ($P < 0.05$) only at 3 atm abs. The restoration of $T_{es}$ was slow and it did not reach control levels during the 15-min recovery. No significant difference in total convective heat flow from the skin was detected between the two environments (52.9 ± 1.2 kcal · m⁻² · h⁻¹ at 1 atm abs vs. 45.8 ± 1.8 kcal · m⁻² · h⁻¹ at 3 atm abs).

**DISCUSSION**

In the present study, we demonstrate that the bradycardia that occurs with acute hyperbaric exposure does not alter cardiovascular responses to orthostatic stress.
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Fig. 2. FBF and laser-Doppler BF\textsubscript{LD}, FVR, TPR, and \(T_a\) responses to HUT at normal atmosphere (1 atm abs, solid line) and 3 atm abs (dashed line). Average BF\textsubscript{LD} during pretilt period are 319 ± 48 mV, and 234 ± 49 mV at 1 and 3 atm abs, respectively. In this figure, BF\textsubscript{LD} is expressed as percent change from pretilt level. Asterisks = \(P < 0.05\) vs. pretilt supine value; daggers = \(P < 0.05\) vs. 1 atm abs value; (\#) = \(P < 0.05\) vs. 1 atm abs value throughout the period.

MAP remained unchanged during HUT and the chronotropic responsiveness (as expressed by \(\Delta HR/\Delta SBP\)) during HUT was the same in both atmospheres. This indicates that there was no difference in orthostatic tolerance at 1 and 3 atm abs. In the present study we used SBP at the brachial artery at heart level. The SBP at the carotid artery can be used, but we assume that the chronotropic responsiveness estimated from the carotid artery will not disagree with that estimated from the brachial artery, because we used the \(\Delta SBP\) rather than the absolute value. Arita et al. (10) observed an orthostatic intolerance in 1 of 3 subjects during a dry saturation dive at 31 atm abs. They postulated inappropriate orthostatic reflexes induced by cardiovascular deconditioning during prolonged high pressure exposure. The orthostatic response observed in the present study may be attributed to a difference in experimental design, inasmuch as the exposure was shorter and the pressure attained was much lower (3 vs. 31 atm abs). A confinement effect that would alter orthostatic tolerance would be minimum in the present study (22), but the purpose was not to
examine cardiovascular deconditioning. It is of interest that the net HR response to HUT was identical in both pressures even though HR was 8 beats/min lower during rest at 3 atm abs. This may indicate that the net sympathetetic outflow to increase HR during tilt is similar in the two environments, but a substantial vagotomy exists at 3 atm abs. This is supported by the fact that the same chronotropic response (ΔHR/ΔSBP) occurred with HUT in both environments. The initial chronotropic response of the baroreceptors is assumed to be mediated by the parasympathetic nervous system (21, 23), whereas when the blood pressure perturbation lasts for longer than 30 s, response mediated by the sympathetic nerve becomes predominant (23).

A significantly lower baseline HR at 3 atm abs was in accordance with previous reports (1–3). In the present study hyperoxia rather than pressure per se was assumed to be an important factor for the development of hyperbaric bradycardia, as reported previously (24). Inspired PO₂ of 477 mmHg in the present experiment was high enough to induce a bradycardia as reported previously (3). It has been suggested that PO₂-induced bradycardia is mediated through the action of the vagus nerves (1, 3).

The reduction of baseline FBF along with an increase in FVR and a reduction in baseline BF₂,₅ at 3 atm abs indicated a cutaneous vasoconstriction compared with the 1 atm abs environment. A density-related increase in convective heat loss from the skin is unlikely to contribute to the vasoconstriction at 3 atm abs because we set ambient temperature at 31°C so that Tₙₖ and Tₑₑ at 3 atm abs would be identical to that at 1 atm abs. Indeed, the convective heat flow was the same in both environments.

Baseline SV and its change during HUT were similar in both environments in agreement with an earlier report (3), but the present HUT-induced reduction in CO was greater at 3 atm abs due to the lower HR. The question arises as to why there was no orthostatic intolerance in the presence of a greater attenuation of CO at 3 atm abs. The most likely explanation is related to the vasoconstrictor response to high oxygen pressure during exposure to 3 atm abs and the augmented vasoconstrictor response to HUT at 3 atm abs.

Bergø et al. (8) measured organ blood flow using microspheres in conscious rats during hyperbaric oxygen exposure to 5 atm abs for 60 min (95% oxygen breathing), and found a marked decrease in tissue blood flow in all organs except for the splanchnic regions. At the same time they observed an increase in TPR. Their observation in the rat agrees with our results where we observed a trend for an increase in TPR at rest in 3 atm abs compared with a 1 atm abs. In addition, we observed an augmented increase in TPR with HUT in the high pressure environment. Inasmuch as the increase in TPR during HUT was greater at 3 atm abs (Fig. 2 and Table 1), it is reasonable to consider that the vasoconstrictor response that occurred in response to HUT is additive with vasoconstriction that occurs with exposure to 3 atm abs. Which vascular bed could be responsible for the increase in TPR during HUT at 3 atm abs? The cutaneous vasculature probably does not contribute to the enhanced TPR response at 3 atm abs because the change in FBF, BF₂,₅, and FVR during HUT was similar at 1 and 3 atm abs. Rowell et al. (25) reported that during lower-body negative pressure (−50 mmHg) one third of the increase in TPR was due to an increase in splanchnic vascular resistance. If the observation by Bergø et al. (8) that PO₂-induced vasoconstriction develops in all organs except for the splanchnic region is applicable to our experiments, we may speculate that the slightly higher baseline TPR at 3 atm abs is achieved by a greater vasoconstrictor response in the skin with little change in the splanchnic area, whereas the cutaneous vasoconstrictor response to orthostasis is
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probably the same at both environments. However, the splanchnic area probably vasoconstricted more at 3 atm abs than at 1 atm abs, leading to a higher TPR. This view is supported by the fact that blood vessels with a higher conductance are more capable of generating a vasoconstrictor response, which results in a redistribution of blood flow (26). Thus, it is conceivable that the vasculature of the splanchnic area plays an important role in the greater increase in TPR in response to HUT at 3 atm abs.

A greater rise in T es during tilt at 3 atm abs also supports the view of a blood redistribution occurring, because T es, a representative temperature of mixed blood in the heart (27), is determined by the proportional amount of returning venous blood coming from peripheral and visceral organs at rest. If part of the returning venous blood coming from the peripheral “cool” tissues decreases with a relative increase in the return of warm blood from the splanchnic area, the temperature of mixed venous blood in the heart will rise (28, 29), as observed during HUT at 3 atm abs.

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