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Am J Physiol Regulatory Integrative Comp Physiol 286:1063-1068, 2004. First published Feb 5, 2004;
doi:10.1152/ajpregu.00653.2003

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Acute hemodynamic responses in the head during microgravity induced by free drop in anesthetized rats

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Submitted 11 November 2003; accepted in final form 30 January 2004

Gotoh, Taro Miyahara, Nobuhiro Fujiki, Kunihiko Tanaka, Tomoko Matsuda, Shuang Gao, and Hironobu Morita. Acute hemodynamic responses in the head during microgravity induced by free drop in anesthetized rats. *Am J Physiol Regul Integr Comp Physiol* 286: R1063–R1068, 2004. First published February 5, 2004; 10.1152/ajpregu.00653.2003.—To examine acute hemodynamic responses to microgravity (μG) in the head, we measured carotid artery pressure (CAP) and jugular vein pressure (JVP) to calculate cephalic perfusion pressure (CPP = CAP – JVP) and recorded images of microvessels in the iris to evaluate capillary blood flow velocity (CBFV) and capillary diameter (CD) in anesthetized rats during 4.5 s of μG induced by free drop. Rats were placed in 30° head-up whole body-tilted (HU, $n = 7$) or horizontal (flat, $n = 6$) position. In the flat group, none of the measured variables was significantly affected by μG , whereas in the HU group, CAP, JVP, and CPP increased, respectively, by 23.4 ± 2.6 , 1.3 ± 0.2 , and 22.9 ± 3.1 mmHg, and CBFV and CD increased, respectively, by 33 ± 8 and $9 \pm 3\%$, showing an increase in capillary blood flow. To further examine the mechanisms underlying these CAP and JVP increases, another experiment was performed in which CAP and JVP were measured in anesthetized rats ($n = 6$) during a postural change from HU to flat. In these animals, the change in JVP was similar to that observed during actual μG , but no change in CAP was seen, indicating that the JVP increase during actual μG is caused by disappearance of the gravitational pressure gradient in the head-to-foot axis, whereas the CAP increase is not. In conclusion, actual μG elicits an increase in CPP due to a greater increase in CAP than JVP, resulting in increased capillary blood flow. Although the increase in JVP is explained by the disappearance of gravitational pressure gradient in the head-to-foot axis as a result of μG , the larger increase in CAP is not.

fluid shift; carotid artery pressure; jugular vein pressure; capillary blood flow

EXPOSURE OF THE HUMAN BODY to microgravity (μG) elicits a “cephalad fluid shift” (2, 5, 10, 18, 21, 24). This phenomenon is associated with the sensation of fullness of the head, facial puffiness, nasal congestion, and a decrease in leg volume reported during actual and simulated μG in humans (14, 15, 19, 22). It is believed that intra- and extravascular fluid moves from the lower body to the thoracic and cephalic regions due to the disappearance of the gravitational pressure gradient in the head-to-foot axis, and this is the key issue in understanding hemodynamics during μG (14). Moore and Thornton (15) reported a 1,026-ml decrease in leg volume in astronauts during spaceflight within the first 6–10 h in orbit. Cephalad fluid shift induces an increase in blood inflow into the thoracic region during μG , i.e., an increase in central venous transmural pressure, left ventricular end-diastolic volume, and cardiac

output in humans (3, 25). As to the cephalic region, although Kawai et al. (13) showed that a simulation of μG by head-down tilt elicited an increase in cerebral blood flow velocity in humans, available information is little about hemodynamic changes during actual μG .

The purposes of the present study were to observe the hemodynamic changes during actual μG in the cephalic region at the macro and micro level and to examine the mechanisms underlying them. For these purposes, we measured the carotid artery pressure (CAP) and jugular vein pressure (JVP), used these values to calculate the cephalic perfusion pressure (CPP), and observed the microcirculation in the iris to estimate the change in capillary blood flow velocity (CBFV) and capillary diameter (CD) in anesthetized rats. The rats were examined in two positions, the horizontal (flat) and 30° head-up whole body-tilted (HU) positions, to evaluate the effects of the disappearance of the gravitational pressure gradient in the head-to-foot axis caused by μG on the hemodynamic responses. Our hypothesis was that in the HU group, the disappearance of the gravitational pressure gradient in the head-to-foot axis would cause the CAP and JVP to increase by the same extent, which is equivalent to the gravitational pressure difference between the heart and the neck, and thus CPP would not change during μG .

METHODS

Male Sprague-Dawley rats ($n = 19$) weighing 320–360 g (12–14 wk old) were used and were maintained in accordance with the “Guiding Principles for Care and Use of Animals in the Field of Physiological Science” of the Physiological Society of Japan. The Animal Research Committee of Gifu University approved the experimental protocol.

Free drop study. On the experimental day, the rats were anesthetized with urethane and α -chloralose (300 and 50 mg/kg body wt ip, respectively). Through a midcervical incision, a polyethylene catheter (PE-50, Becton Dickinson, Sparks) was inserted into the internal carotid artery via the proximal portion of the external carotid artery to measure the CAP, and the external carotid artery was ligated. A second catheter was inserted into the jugular vein via a small branch of it to measure the JVP, and the small branch was ligated. Both catheters were exteriorized at the back of the neck and connected to pressure transducers (MP5200, Baxter, Deerfield), each of which was fixed at the same level as the tip of the corresponding catheter, because a difference in level between the two would result in a gravitational pressure difference on a change in gravity (7, 8). The signals from the transducers were transmitted to amplifiers (AP-621G, Nihon Kohden, Tokyo), and both signals and the gravity (G) level were recorded using a DAT data recorder (RD-145T, TEAC, Tokyo) for later analysis.

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Images of the microvessels of the iris were obtained using a charge-coupled device (CCD) camera (PX-30KST, Primetech Engineering, Tokyo) installed on a microscope with a $\times 4$ objective lens (Olympus, Tokyo). The iris was epi-illuminated using a light source unit (KTX-100R, Kenko, Tokyo). After the position of the microscope was adjusted, silicon oil (Nacakai Tesque, SH-550, Kyoto) was dropped onto the eye surface to avoid drying out, and the CCD camera image was recorded on a digital video recorder (DCR-TRV30, Sony, Tokyo).

Free drop experiments were performed at the Microgravity Laboratory of Japan (MGLAB, Toki, Japan; <http://www1.ocn.ne.jp/~mglab/>). The free drop zone was 100 m in length and equipped with a drop tube of 1.5 m in diameter, inside which the free drop capsule (outer diameter 900 mm, height 2,100 mm) fell to the brake zone. The tube was evacuated to eliminate aerodynamic resistance during fall, but air pressure and temperature inside the capsule were kept constant at atmospheric pressure and 24°C. The capsule was initially retained by an electromagnet at the top of the drop tube, and then the electromagnet was switched off and free drop started. Within 100 ms after the start of the drop, gravity inside the capsule fell below 0.01 G. This μG condition was maintained for ~ 4.5 s and then was followed by hypergravity, due to braking. Each rat was fixed in the prone posture using a skull-locking device. The rats were placed in the horizontal (flat group; $n = 7$) or 30° HU position (HU group; $n = 6$). As shown in Fig. 1, in the HU group, gravitational pressure gradient exists in both the head-to-foot axis and back-to-abdominal axis, whereas in the flat group, gravitational pressure gradient exists only in the back-to-abdominal axis but not in the head-to-foot axis during 1 G. During μG , all of these gradients disappear in both groups. By examining both positions, the effects of the gravitational pressure gradient in the head-to-foot axis on the response of the cephalic circulation to μG can be estimated (8).

After the free drop, the recorded data on the DAT were played back and sampled using an analog-to-digital converter (PowerLab, ADInstruments, Castle Hill, NSW, Australia) at a rate of 100 samples/s. The data for the G level, CAP, and JVP were averaged over 0.5 s. A total of 18 data points, consisting of 9 data points during the 1-G control period immediately before drop and 9 data points during μG , were collected for each rat. The CPP was calculated using the equation $\text{CPP} = \text{CAP} - \text{JVP}$.

Time-sequence images of the microcirculation in the iris were analyzed using the freeze-frame method (27). For each rat, the microvessels were identified and their diameters were measured. To assess blood flow at the capillary level, microvessels with diameters $> 25 \mu\text{m}$ were excluded from the following analysis. For each microvessel, the CBFV was calculated from the distance moved by blood cells, which was followed over two to four frames at a frame rate of 29.9 frames/s (Fig. 2). Throughout the control 1-G and μG

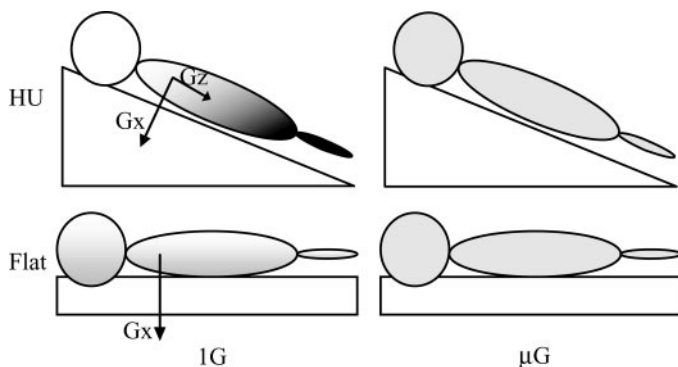


Fig. 1. Relationship between the rats position and gravitational pressure (G) gradient. μG , microgravity; HU, 30° head-up whole body-tilted position; flat, horizontal position; G_z , head-to-foot axis; G_x , back-to-abdominal axis. See METHODS for details.

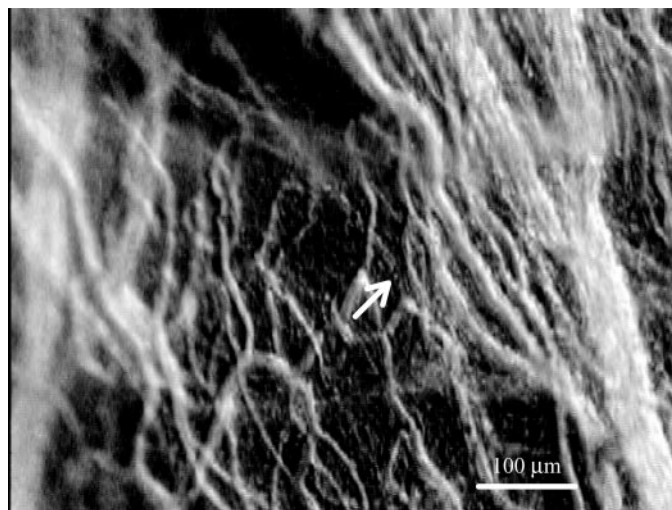


Fig. 2. Representative image of the microcirculation in the iris in an anesthetized rat, using the freeze-frame method. Blood cells (arrow) were tracked over 2–4 frames to calculate the capillary blood flow velocity.

periods, as many data points as possible were collected for the CBFV and CD. To normalize the variation in the CBFV and CD between capillaries, each data point was expressed as a percentage of the averaged value during the control 1-G period.

Each rat was tested only once and in only one position. Results are expressed as means \pm SE. For statistical analysis, the values for each variable during μG were divided into those during the early period (0–2.0 s) and the late period (2.0–4.5 s) of μG . The values of variables during μG were compared with those during the 1-G period using Friedman's test. The significance level was set at $P < 0.05$.

Postural change study. To further examine the mechanisms involved in the CAP and JVP changes observed in the free drop experiment, another experiment was performed. While the animals were under anesthesia, the catheters used to measure the CAP and JVP were implanted as described above, and another catheter to measure the aortic pressure (AoP) was inserted into the aorta immediately below the diaphragm through the femoral artery. The experimental setup was the same as for the free drop experiment. The rat was placed on a cork board in the 30° HU position. About 10 min later, the control data were collected, and then the position of the rat was changed to flat. The postural change induced the disappearance of the gravitational pressure gradient in the head-to-foot axis and cephalad fluid shift in the same way as in the HU group of the free drop experiment. After the experiment, the data were averaged over each of the 5 s before postural change and of the 10 s after postural change. The values for the variables after the postural change were compared with the control values using Friedman's test. The significance level was set at $P < 0.05$.

RESULTS

A total of 13 free drops (13 different rats), consisting of 7 in the HU position and 6 in the flat position, was performed. The averaged G level during free drop was $-3.3 \times 10^{-3} \pm 0.0 \times 10^{-3}$ G. In the HU group, the CAP in one rat and the JVP in another could not be measured due to obstruction of the catheter.

Figure 3 shows typical G level, CAP, and JVP responses to free drop in HU (Fig. 3A) and flat (Fig. 3B) rats. The G-level traces showed a smooth transition from 1 G to μG and that μG lasted 4.5 s in both rats. In the HU rat, the CAP increased

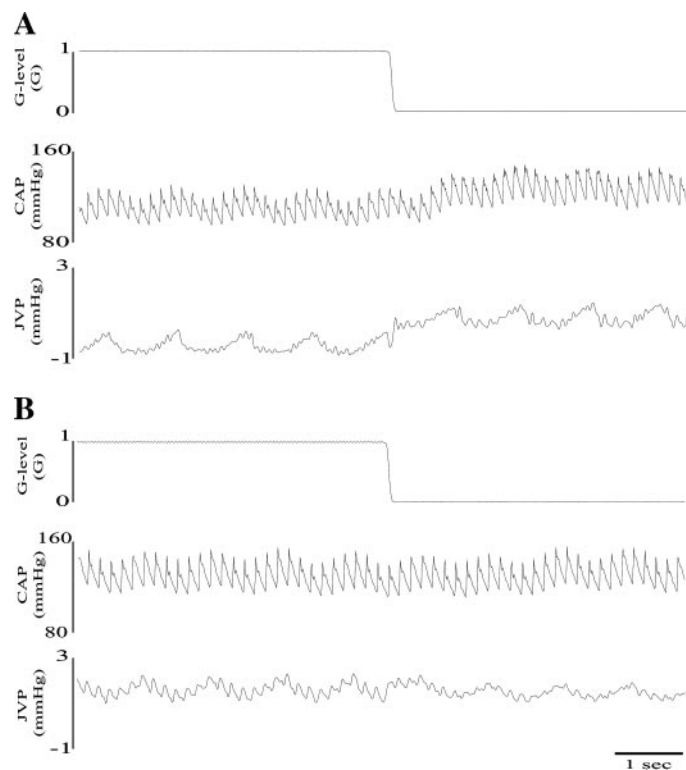


Fig. 3. Original recordings of gravity (G) level, carotid artery pressure (CAP), and jugular vein pressure (JVP) responses to μ G induced by free drop in anesthetized rats in the 30° HU (A) and horizontal (flat; B) positions.

gradually from 108 to 125 mmHg during μ G, and the JVP increased from -0.5 to 0.8 mmHg. The increase in the CAP (17 mmHg) was much greater than that in the JVP (1.3 mmHg). In contrast, in the flat group rat, the CAP and JVP did not change during μ G.

The averaged data for the CAP, JVP, and CPP in the HU and flat groups are shown in Fig. 4 and Table 1. In the HU group, the CAP started to increase at the onset of μ G and reached a plateau 1.5 s later. Statistical analysis (Table 1) showed that the difference between the CAP in the control period and that during late μ G was significant. In the flat group, the CAP was stable throughout μ G. The JVP increased significantly during μ G in the HU group, whereas in the flat group it was unaffected. In the HU group, because the increase in CAP was greater than that in JVP, the CPP increased significantly during late μ G, whereas in the flat group, it did not.

The microcirculation data are presented in Fig. 5 and Table 2. During the control 1-G period, there was no statistically significant difference in the diameter and blood flow velocity of the capillaries between the HU and flat groups (Table 2). In the HU group, both the CBFV and CD increased gradually, the changes reaching statistical significance during late μ G (CBFV $133 \pm 8\%$ and CD $109 \pm 3\%$). In contrast, in the flat group, the CBFV and CD did not change during μ G.

Figure 6 and Table 3 show the averaged data for the AoP, CAP, and JVP responses to the postural change from HU to flat. After the postural change, the AoP and CAP did not change, but the JVP increased significantly by about the same amount as in the HU group of the free drop experiment.

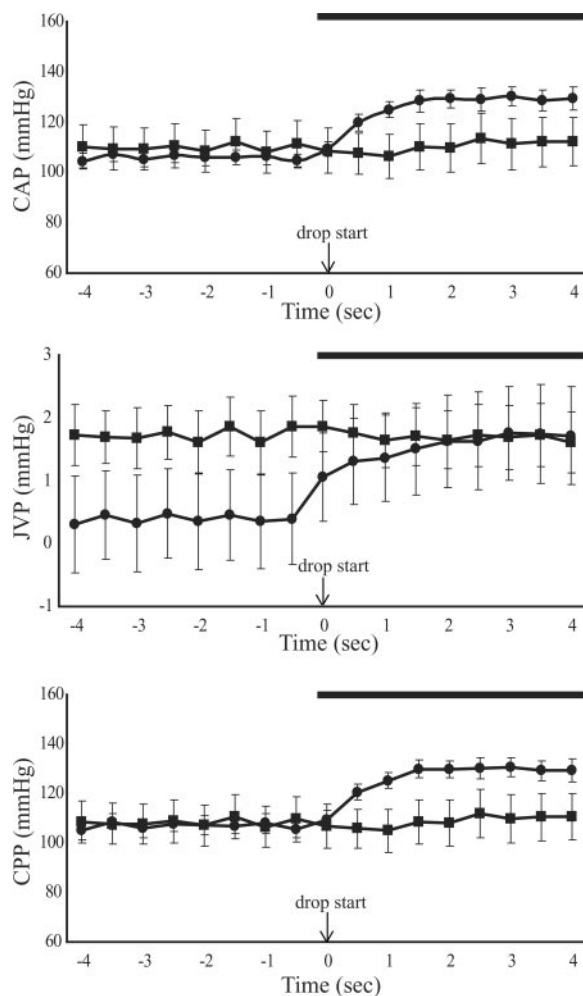


Fig. 4. Averaged CAP, JVP, and cephalic perfusion pressure (CPP) responses to μ G induced by free drop in anesthetized rats in the 30° HU (●, $n = 7$) and horizontal (flat; ■, $n = 6$) positions. Each data point represents the mean \pm SE. Horizontal bar represents the period of μ G.

DISCUSSION

The present study is the first in which the CPP has been calculated by directly measuring the CAP and JVP and the microcirculation observed in the head during actual μ G. The

Table 1. Statistical analysis for the free drop experiment

	<i>n</i>	Control	Early μ G	Late μ G
CAP, mmHg				
HU	6	105.9 \pm 3.0	120.7 \pm 3.2	129.3 \pm 4.1*
Flat	6	110.1 \pm 8.7	108.3 \pm 8.7	111.8 \pm 9.9
JVP, mmHg				
HU	6	0.4 \pm 0.7	1.3 \pm 0.7	1.7 \pm 0.8*
Flat	6	1.7 \pm 0.5	1.7 \pm 0.4	1.7 \pm 0.5
CPP, mmHg				
HU	5	106.9 \pm 3.5	121.3 \pm 3.2	129.8 \pm 4.0*
Flat	6	108.3 \pm 8.5	106.5 \pm 8.5	110.1 \pm 9.5

Values are means \pm SE for carotid artery pressure (CAP), jugular vein pressure (JVP), and cephalic perfusion pressure (CPP) in anesthetized rats in the 30° head-up whole body-tilted (HU) or horizontal (flat) positions. Data were averaged over the 4.5 s immediately before free drop (control) or over the period of 0–2.0 s [early microgravity (μ G)] or 2.0–4.5 s (late μ G) after onset of free drop. * $P < 0.05$ vs. control (Friedman's test).

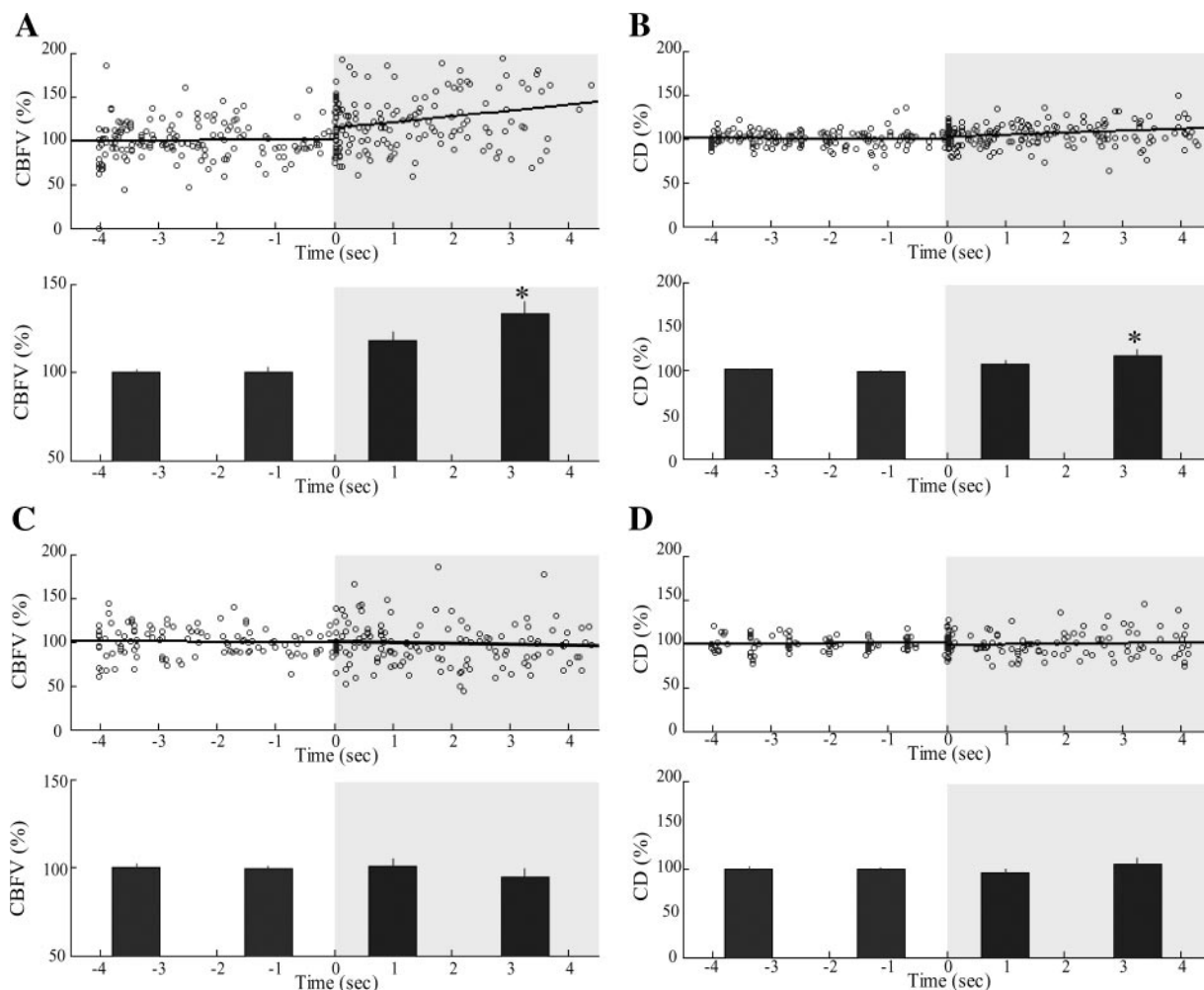


Fig. 5. Original measurements and averaged data for capillary blood flow velocity (CBFV, *A* and *C*) and capillary diameter (CD, *B* and *D*) responses to μG induced by free drop in anesthetized rats in the 30° HU (*A* and *B*) and horizontal (flat; *C* and *D*) positions. Each bar represents the mean \pm SE for 22 capillaries in rats in the HU position and 16 in the flat position. Gray background represents the period of μG . * $P < 0.05$ vs. control (Friedman's test).

major findings of the present study are that 1) the CAP and JVP increased during μG in the HU group; 2) because the increase in the CAP was greater than that in the JVP, the CPP in the HU group increased during μG ; 3) the CBFV and CD increased during μG in the HU group; 4) none of these variables was affected by μG in the flat group; and 5) although the JVP increase in the HU group was reproduced by the postural change, the CAP increase was not.

In the present study, an increase in JVP during μG was seen in the HU group. This is consistent with results from human studies that imply that an increase in JVP occurs during

spaceflight, i.e., increased blood filling of the jugular vein and a 30% increase in jugular vein diameter (11, 12). The key issue in understanding the increase in JVP is that it was observed only in the HU position. As mentioned in METHODS, the gravitational pressure gradient in the head-to-foot axis that exists during the 1-G period only in those animals in the HU position disappears during μG . This results in an increase in venous pressure at points in the body at a level higher than the hydrostatic indifferent point, defined at the level at which no change in gravitational pressure occurs after a change in gravity. Supporting the idea that the JVP change in HU rats on going from 1 G to μG was caused by the disappearance of the gravitational pressure gradient in the head-to-foot axis, the observed change in JVP was 15 mmHg (1.1 mmHg), which approximately corresponds to the height difference between the heart and jugular vein in HU rats. Furthermore, the fact that the JVP change was reproduced by the postural change also supports this assumption because it can be supposed that the postural change elicits the disappearance of gravitational pressure gradient in the head-to-foot axis in the same way as the actual μG .

Table 2. Control data for the analyzed microvessels

Group	<i>n</i>	Diameter, μm	Flow Velocity, $\mu\text{m}/\text{sec}$
HU	22	11.7 \pm 0.7	185 \pm 22
Flat	16	13.0 \pm 1.2	168 \pm 16

Values are means \pm SE for the diameter and flow velocity of the analyzed microvessels during the control 1-G period in anesthetized rats in the 30° HU or horizontal (flat) positions.

The marked increase in the CAP seen in the HU group was unexpected because we hypothesized that the CAP and JVP would increase by the same extent in the HU group. To understand the different extent of increase in CAP and JVP, the static component (generated by the gravity) and dynamic component (generated by the heart pumping) of the pressure should be considered. As mentioned in the previous paragraph, the increase in JVP can be explained by the change in the static component. On the other hand, it can be supposed that dynamic component as well as the static component of the pressure are increased in the arterial system. It is known that the dynamic pressure of the artery is the product of the cardiac output (CO) and total peripheral resistance, and the CO is determined by the intersection of the CO curve and venous return (VR) curve (9). In the HU group of the free drop experiment, the disappearance of the gravitational pressure gradient in the head-to-foot axis will elicit an upward shift of the VR curve. Furthermore, effect of the intrathoracic (or intrapleural) pressure may be important. We previously demonstrated that the intrathoracic pressure decreased during μG in HU rats (16, 17). A decrease in esophageal pressure, used as an index of intrathoracic pressure, has also been seen in humans during parabolic flight (25). Computer-based simulation indicates that a decrease in in-

Table 3. Statistical analysis for the postural change experiment

	Control (HU)	Flat
AoP, mmHg	103.8 \pm 3.5	104.6 \pm 2.6
CAP, mmHg	102.1 \pm 3.1	105.4 \pm 2.3
JVP, mmHg	0.4 \pm 0.3	1.3 \pm 0.3*

Values are means \pm SE for the aortic pressure (AoP), CAP, and JVP in controls and after a postural change from the 30° HU to the horizontal flat position in anesthetized rats ($n = 6$). Data were averaged over the 5 s immediately before posture change (control) and over the 10 s immediately after posture change (flat). * $P < 0.05$ vs. control (Friedman's test).

trathoracic pressure elicits a leftward shift in the CO curve (26). Thus multiplier effects of the upward shift of the VR curve and leftward shift of the CO curve may elicit the considerable increase in dynamic component of the arterial pressure. In this context, the upward shift in the VR curve alone, which will occur in the postural change from HU to flat, is not enough to elicit the CAP increase.

Because the CAP increased more than the JVP in the HU group, the CPP increased during μG . Such a change may be reflected by the microcirculation in the head. We chose the iris as the organ in which to observe the microcirculation, because we were interested in effects on the upper body, especially the head, and the iris is the only organ in which the microcirculation can be observed without invasive procedures. Our results showed an increase in CBFV with a slight increase in CD during μG in the HU group, showing an increase in capillary blood flow. Although there are no reported studies on the microcirculation in the head during actual μG , simulated μG experiments in humans have shown an increase in skin blood flow in the forehead and cheek and an increase in capillary blood pressure (1, 19, 20). Generally the relationship between blood flow, perfusion pressure, and vascular resistance in an organ follows Ohm's law: blood flow = (perfusion pressure)/ (vascular resistance). It is well known that in some organs (e.g., the brain and retina), a change in perfusion pressure within a certain range does not cause change in blood flow due to the automatic regulation of vascular resistance, i.e., autoregulation, in humans and animals. However, in others, e.g., the iris (animal results) and head skin (human results), autoregulation of blood flow is weak (1, 4, 6, 23). In the second group, an increase in perfusion pressure elicits an increase in blood flow, as shown in the present study. Assuming that the changes observed in the present study occur also in humans, they may cause leakage of the serum from the capillaries into the interstitial space and thus the facial symptoms experienced by astronauts during spaceflight.

In conclusion, in rats in the HU position, μG elicits an increase in CPP due to a greater increase in CAP than in JVP, resulting in increased capillary blood flow in those organs in the head lacking autoregulation. Although the increase in JVP is explained by the disappearance of the gravitational pressure gradient in the head-to-foot axis during μG , the increase in CAP is not.

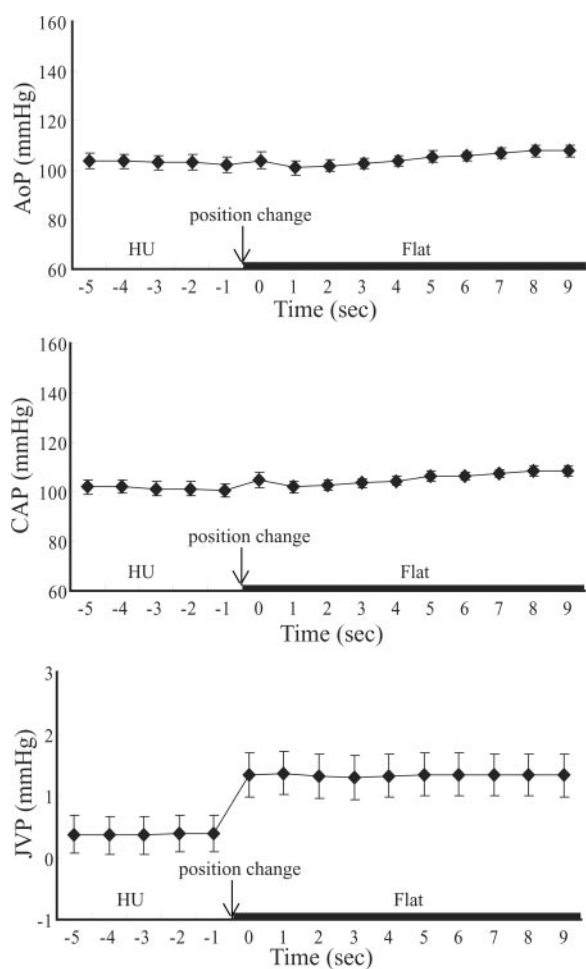


Fig. 6. Averaged aortic pressure (AoP), CAP, and JVP responses to a postural change from the 30° HU to the horizontal (flat) position in anesthetized rats ($n = 6$). Each data point represents the mean \pm SE. Horizontal bar represents the period of flat position.

ACKNOWLEDGMENTS

We thank Dr. T. Kiyooka for technical advice.

GRANTS

This study was supported by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and a "Ground Research for Space Utilization" research grant from the National Space Development Agency of Japan and the Japan Space Forum.

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