Mechanisms of Increased Intracranial Pressure in Rabbits Exposed to Head-Down Tilt

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Abstract: Changes in intracranial pressure (ICP) resulting from head-down tilt (HDT) were studied in rabbits, and a possible role of edema formation in the change of ICP was examined. Animals were anesthetized with pentobarbital sodium and artificially ventilated. ICP was continuously monitored through a catheter inserted into the subarachnoid space. It increased depending on the tilt angle and decreased when the tilt angle was reduced. ICP elevated from 4.6 ± 0.7 mmHg (mean $\pm$ standard error of the mean) at horizontal prone position to 13.7 ± 1.0 mmHg immediately after the onset of 45° HDT and gradually reduced toward the pre-HDT baseline in the next 8 h. ICP decreased below the pre-HDT

baseline value immediately after returning to the horizontal prone position, and gradually increased toward the baseline during the 2 h of recovery period. Histological examination (HE stain) demonstrated that exposure to 8 h of HDT did not cause remarkable edema in either the gray matter or the white matter in rabbits. Water content and specific gravity of brain tissues both were increased in the HDT group in comparison with the control group. These results suggest that edema formation plays little role in the elevation of ICP during the acute phase of HDT in rabbits. [Japanese Journal of Physiology, 48, 63–69, 1998]

Key words: microgravity, head-down tilt, intracranial pressure, brain edema, cerebral circulation.

A microgravity environment causes a redistribution of body fluids. One direct effect of exposure to actual or simulated microgravity is the cephalad fluid shift [1–5]. Astronauts often experience headaches [6] and space motion sickness during spaceflight [7]. Although the mechanisms of the symptoms are poorly understood, they may be attributed, in part, to the changes in cerebral circulation and intracranial pressure (ICP).

The effects of microgravity on the cardiovascular system may be simulated by head-down tilt (HDT) on Earth [8, 9]. Keil and co-workers [10] reported that intracranial pressure elevated in anesthetized monkeys exposed for 15 min to 6° HDT. Murthy *et al.* [11] demonstrated an increase of ICP during the acute stages of 6 and 15° HDT in humans by a noninvasive tympanic membrane displacement technique. The elevated ICP during HDT might be attributed to brain

edema as well as to venous engorgement in the brain. During HDT, venous pressure in the head increases because of hydrostatic pressure [12,13], which would cause venous engorgement. Increased venous pressure also plays an important role in the elevation of capillary pressure. Parazynski and colleagues [13] demonstrated elevation of the capillary pressure in the head of human subjects during HDT. Wen *et al.* [14] showed disruption of the blood-CSF barrier because of elevated arterial pressure during 90° HDT in rabbits. These observations suggest that exposure to HDT may increase capillary filtration and produce brain edema. In fact, a morphological study showed vessel dilatation and perivascular edema in the monkey brain after 7 and 19 d of 6° HDT [15]. It was not demonstrated, however, when the edema formation started after the onset of HDT.

Previous reports demonstrated that ICP increased

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within several minutes after the onset of simulated microgravity [10,11], and information on ICP response to HDT for prolonged periods is not available, except in our previous report using rats [16]. Only a small increase (about 2 mmHg) of ICP was observed in rats because of the little effect of hydrostatic pressure resulting from the small size of the animal body. Thus in this study, we used rabbits to examine the effect of greater hydrostatic pressure than in rats. The circulation in the head alters remarkably within 12 h of 6° HDT [17]. Therefore it would be interesting to learn 1) how ICP responds to prolonged HDT in rabbits, 2) when brain edema appears during HDT, and 3) whether brain edema contributes to increased ICP during the early stage of HDT.

Thus the two purposes of this study were 1) to examine the time course of ICP during 8 h of 45° HDT in rabbits and 2) to demonstrate whether brain edema occurs during the 8 h of HDT by investigating morphological changes and measuring water content and specific gravity of the brain tissue. We hypothesized that exposure to HDT causes brain edema within 8 h, which is responsible, in part, for the elevation of ICP.

METHODS

All procedures used in the present study were reviewed and approved by the Committee for Animal Experimentation in the Faculty of Medicine, Tottori University, Japan, and conformed to all standards set forth in the Guiding Principles for the Care and Use of Animals approved by the Council of the Physiological Society of Japan.

Experiment 1. Twenty adult albino rabbits of both sexes, weighing 2.4–3.2 kg, were used in the experiments. The rabbits were fasted overnight and anesthetized with intravenous injections of 25 mg/kg pentobarbital sodium (Nembutal, Abbott Laboratories, North Chicago, Ill.). An additional dose (1 mg/kg/h) of pentobarbital sodium was administered through a polyethylene tube inserted into the right femoral vein with a syringe pump (STC-521, TERUMO, Tokyo) throughout the experiment. Each rabbit was paralyzed with pancuronium (Mioblock, Organon, Oss, The Netherlands) (initial dose of 0.2 mg/kg and additional doses as necessary, I.M.) and artificially ventilated (60 cycle/min, 5 ml/kg) with room air by a mechanical ventilator (SN-480-6, Shinano, Tokyo) to maintain P_{aCO_2} at 30–40 mmHg. Rectal temperature was maintained from 38 to 40°C by using a heating pad. For the measurement of arterial pressure and the blood gas analysis (model 1306, Instrumentation Laboratory, Milano, Italy), the right

femoral artery was cannulated with a polyethylene tube filled with a physiological salt solution (Otsuka, Tokyo) containing 10 IU/ml of heparin (Heparin Sodium Injection-N, Shimizu, Japan). Before and 4 h after the onset of HDT, 0.3 ml of arterial blood was drawn through a three-way stopcock to measure P_{aCO_2} . The same amount of physiological salt solution was injected to replace the blood. To confirm the hydrostatic effect of tilting on systemic circulation, the arterial pressure was measured by a pressure transducer (TP-400T, Nihon Kohden, Tokyo), which was secured at the same height as the tip of the arterial catheter, and recorded on a thermal array recorder (RTA-4100, Nihon Kohden).

After these procedures were completed, the rabbits were mounted in a stereotaxic instrument that can be rotated in pitch. A midline scalp incision was made and a burr hole with a diameter of 3 mm was opened in the left side of parietal bone 6 mm posterior to the bregma, 2.5 mm lateral to the sagittal suture. A tiny hole was made in the dura mater with a 26 G needle. A polyethylene catheter (3 Fr) filled with artificial cerebrospinal fluid (NaCl 132.8 mM, $NaHCO_3$ 24.6 mM, urea 6.7 mM, glucose 3.7 mM, KCl 3.0 mM, $CaCl_2$ 2.0 mM, and $MgCl_2$ 0.7 mM) was bent and inserted into the subarachnoid space. The holes in the dura mater and the parietal bone were closed by using chemical glue so that cerebrospinal fluid did not escape through them. A pressure transducer (TP-400T, Nihon Kohden) was connected to the catheter and fixed at the same height as the catheter tip. The subarachnoid pressure, or ICP, exhibited fluctuations consisting of two components: 1) small amplitude waves with high frequency because of arterial pulsations and 2) high amplitude waves with low frequency because of respiratory movement. Data were to be discarded if these fluctuations were not observed. In four rabbits, the relationship between ICP and tilt angle was examined. The animals were placed prone (0°), tilted head down successively at 15, 30, 45, 60, and 75°, and returned to 60, 45, 30, 15, and 0°. They were kept in each posture for 5 min. In the other 16 rabbits, the time course of ICP before, during, and after 8 h of 45° HDT was observed. At the end of the 60 min baseline measurement in horizontal prone position, the rabbits ($n=8$) were tilted at 45° head-down for 8 h, then returned to the horizontal position for 2 h for observation of the recovery. The control animals ($n=8$) remained in the prone position throughout the experiment.

Experiment 2. Brain tissues were histologically examined in 12 rabbits to observe whether the edematous change occurs during 8 h of HDT. All procedures

for surgical preparations were the same as in Experiment 1 except that ICP was not measured in this group. The animals were divided into 4 subgroups. The brains of experimental animals were removed after 4 ($n=3$) or 8 h ($n=3$) of 45° HDT, and 2 h after 8 h of HDT ($n=3$). The brains of control animals ($n=3$) were removed 8 h after the start of the experiment, during which the rabbits were kept in horizontal prone position. These animals were sacrificed with an overdose (100 mg/kg) of pentobarbital sodium. The brains were fixed in 10% formalin and embedded in soft paraffin. From coronal blocks at the central sulcus, sections 4 μ m thick were cut, and brain tissues stained with hematoxylin-eosin were subjected to regular light microscopy. Edema formation was estimated according to generally accepted criteria [18].

Experiment 3. Eight rabbits were used for measurements of specific gravities and water content in the brain tissues. Specific gravities were measured by the technique of Marmarou *et al.* [19]. Briefly, a gradient column was made in 250 ml fluid mixture consisting of bromobenzene (Kanto Chemical Co., Inc. Tokyo) and kerosene (Kanto Chemical), whose specific gravities are 1.065 and 1.035. The brain was removed from the animals after exposure to 8 h of HDT ($n=4$) or from control animals ($n=4$) kept in horizontal prone position for 8 h. A small piece (1 mm³ or less) of gray matter or white matter from the parietal lobe was dropped into the fluid column, and its final position was determined 5 min later. The relationship between depth in the gradient column and specific gravity was calibrated by using droplets of standard solutions of K₂SO₄ dried overnight at 100°C in a standard oven. Water content was calculated by means of a classic desiccation method [20, 21]. Samples, consisting of gray and white matter and weighing from 150 to 350 mg, were taken from the frontal lobe. After determination of their wet weight by using a sensitive electronic scale (AG245, Mettler-Toledo, Greifensee, Switzerland), they were dried at 100°C in a standard oven until the weight reached a constant value. The percent of water content was calculated according to the following equation: % water content = [(tissue wet weight - tissue dry weight)/tissue wet weight] $\times$ 100.

Data analysis. Data for ICP were averaged over 120 s at the following time points: 0.5 h and just (within 3 min) before HDT; immediately (within 3 min), 2, 4, 6, and 8 h after the onset of HDT; immediately (within 3 min) and 2 h after the end of HDT. Data are expressed as means $\pm$ SEM. The data were statistically analyzed by Student's *t*-test for unpaired observations between HDT and control groups. Statistical significance was defined as $p < 0.05$.

Fig. 1. Relationship between ICP and tilt angle ($n=4$). Rabbits were kept in each position for 5 min.

Fig. 2. Typical recording of ICP at the onset of 45° HDT (a), after 4 h of HDT (b), and at the cessation of HDT (c).

RESULTS

Experiment 1

In the experiment to determine the effect of tilt angle, ICP was 5.5 ± 1.3 mmHg at horizontal prone position (0°) in four rabbits (Fig. 1), and the value changed quickly and reached a new steady state value within 30 s. It increased, depending on the tilt angle, to 15.0 ± 1.0 mmHg at 45° HDT and 18.7 ± 0.9 mmHg at 75° HDT; it then decreased when the tilt angle was reduced. After returning to horizontal posture, ICP (4.1 ± 0.5 mmHg) was not significantly different from the initial control value.

A typical recording of ICP at the onset of 45° HDT, after 4 h of HDT, and at the cessation of HDT is shown in Fig. 2, and the values of ICP of the control and the HDT groups are shown in Fig. 3. In the control group ($n=8$), ICP did not change significantly throughout 11 h of experiment. The pre-HDT baseline value in the HDT group ($n=8$) was not significantly different from that in the control group. In the HDT group, ICP increased from 4.6 ± 0.7 to 13.7 ± 1.0 mmHg immediately after the onset of 45° HDT. It gradually decreased during HDT, but remained significantly higher than the value in the control animal until

4 h after the onset of HDT. When the rabbits were returned to the horizontal prone position, ICP decreased immediately below the control value at the same time point. It increased slowly toward the control value during 2 h of recovery.

Table 1 shows changes in mean femoral arterial pressure and arterial CO₂ tension before, during, and after 8 h of HDT ($n=8$). The femoral arterial pressure decreased significantly ($p<0.005$) during HDT as a result of hydrostatic effect and returned to the pre-HDT baseline level during horizontal recovery. The arterial CO₂ tension did not change significantly during HDT.

Experiment 2

The absence or presence of edema was assessed by light microscopic examination in the gray and white matter in the parietal lobes of control and HDT rabbits. Figure 4 shows microscopic sections of gray matter of control (upper panel) and HDT (lower panel) rabbits. Edematous changes such as distention of perivascular and pericellular spaces and vacuolar appearance of the gray matter neuropil were not observed in any section from 4 subgroups. Neither was

Fig. 3. Change in ICP in rabbits before, during, and after 8 h of 45° HDT (○, $n=8$). The pre-HDT baseline value and the post-HDT value were obtained at horizontal prone positions. Rabbits in the control group (●, $n=8$) remained in the horizontal prone position throughout the experimental period. *Significantly different from the corresponding value in the control group at the identical time point, $p<0.05$. The vertical bars indicate standard error of the mean. HDT, head-down tilt.

remarkable edema observed morphologically in the white matter of control and experimental rabbits.

Experiment 3

Water content and specific gravities in brain tissues were measured in control ($n=4$) and HDT ($n=4$) rabbits. The weight of brain tissue in the standard oven reached a constant value by 48 h. The water content of HDT rabbits was $81.42\pm0.03\%$, being significantly higher ($p<0.05$) than that of control rabbits, $80.75\pm0.27\%$. Specific gravities of gray and white matter in experimental and control animals are shown in Table 2. In gray matter and in white matter, specific gravities in the experimental group were significantly higher than in the control group.

Fig. 4. Coronal sections of gray matter from (upper) control and (lower) experimental rabbits (8 h after exposure to 45° HDT). Edematous changes are not observed in either section (hematoxylin and eosin, $\times 100$).

Table 1. Changes in mean arterial pressure and P_{aCO_2} before, during, and after 8 h of HDT.

	<i>n</i>	Pre	During ^a	Post
Mean arterial pressure (mmHg)	8	98.9 $\pm$ 3.1	86.9 $\pm$ 1.5*	95.0 $\pm$ 2.5
P_{aCO_2} (mmHg)	8	35.8 $\pm$ 1.5	36.6 $\pm$ 2.2	

n: number of animals. ^a At 4 h after the onset of HDT. * $p<0.05$ vs. pre-HDT value.

Table 2. Water content and specific gravity of brain tissues in control and HDT rabbits.

	<i>n</i>	Control	HDT
Water content (%)	4	80.75±0.03	81.42±0.27*
Specific gravity			
Gray matter	4	1.0375±0.0002	1.0411±0.0006*
White matter	4	1.0368±0.0002	1.0391±0.0005*

n: number of animals. * $p < 0.05$ vs. control group.

DISCUSSION

The present results demonstrated that mean ICP increased from 4.6 ± 0.7 mmHg in the horizontal prone position to 13.7 ± 1.0 mmHg immediately after exposure to 45° HDT. This increase is much greater than that (about 2 mmHg) observed in rats exposed to 45° HDT [16]. It may be attributable to the difference in body size, since the effect of hydrostatic pressure during HDT must be greater in larger animals than in smaller ones. Other possible explanations for the big difference may include the difference in the measuring site of ICP (cisterna magna in rats vs. intracranial subarachnoid space in rabbits). After the initial elevation, ICP gradually fell toward the pre-HDT baseline value, which was also found in rats [16]. The difference in the time course of ICP during 8 h of HDT between rabbits and rats was that ICP began to rise again after 3 h of HDT in rats [16], whereas in rabbits a second rise in ICP was not observed.

One possible factor for the elevation of ICP might be the formation of edema in the brain tissue. A morphological study shows that exposure to 6° HDT for 7 d produces perivascular edema in the monkey brain [15], but it does not clarify when the edema formation started. Parazynski and colleagues [13] demonstrated that 8 h of HDT at 6° elevate capillary pressure in the head and decrease colloid osmotic pressure in human subjects, which increase capillary filtration and are responsible for facial edema and nasal congestion. However, it is not clear that these hemodynamic changes produce edema during 8 h of HDT in the brain where blood-brain barrier protects tissues from edema formation. Thus in the present study, the absence or presence of brain edema was examined in rabbits exposed to 8 h of 45° HDT. Histological examination did not demonstrate remarkable edema either in gray matter or in white matter. However, this does not necessarily indicate an absence of edema because a histological assessment of mild or moderate degrees of edema can be very difficult. Although it is well established that water content increases in the brain tissue, which is edematous, no correlation was observed

between the water content and the histological grading for brain edema [18]. Therefore we estimated brain edema chemically as changes in water content and specific gravities. The present results show that HDT increases water content in the brain tissue by 8 h after its onset. This may imply the presence of edema. It has also been shown, however, that specific gravities of gray and white matter also increased during exposure to HDT (Table 2). If the increased water content is due to the formation of edema, the specific gravities of the tissues should be decreased, since the specific gravity of water or plasma is smaller than that of brain tissue. Thus it seems more reasonable to attribute the increased water content to an accumulation of whole blood, whose specific gravity is greater than that of brain tissue. The accumulated blood is probably in the intravascular compartment, since hemorrhage was not observed in the brain tissue examined in this study. It is therefore suggested that edema formation plays but little role in the elevation of ICP during 8 h of HDT in rabbits. It is also supported by the decrease of ICP below the pre-HDT baseline value immediately after return to the horizontal prone position. The reduction of ICP may have been delayed if a great amount of brain edema had been produced by exposure to 8 h of HDT.

The initial increase in ICP seems to result from venous engorgement in the brain tissue and the CSF shift from the spinal subarachnoid space into the intracranial subarachnoid space. HDT elevates venous pressure in the head [12,13], which results in an increase in blood volume in the intracranial veins. It is also known that a large amount of CSF shifts because of hydrostatic effect caused by postural change [12, 22]. Since these shifts occur within the same compartment of fluid, i.e., within blood vessels or subarachnoid spaces, it is reasonable that they contribute to the initial rise in ICP, which was observed immediately after the onset of HDT. The subsequent decrease in ICP during HDT is presumably a result of the enhanced absorption of CSF mainly through arachnoid villi, which is a common mechanism for reducing ICP when it elevates above normal.

In previous animal experiments, various angles of HDT or tail suspension have been employed to simulate microgravity on Earth. Changes in ICP during HDT have not been investigated in rabbits, except for our previous study in which the tilt angle was 45° [23]. In the present study, the relationship between ICP and the tilt angle was examined in four rabbits. The head down at 45° increased ICP by 9.4 mmHg, compared with the value at 0°. The greater the tilt angle, the more the change in ICP. In human subjects, an increase in ICP produced by 6° HDT was estimated at about 15.5 mmHg by means of the tympanic membrane displacement technique [11]. The ICP in monkeys elevated from -6.3 mmHg in an upright sitting posture to +5.3 mmHg at 6° HDT [10]. Thus exposure to 45° HDT causes an increase of ICP that is slightly less in rabbits than in human subjects and monkeys going from upright to 6° HDT. In preliminary experiments, we tried 60° HDT in rabbits. Prolonged exposure (more than a few hours) to 60° HDT, however, decreased mean arterial pressure at heart level. On the other hand, 45° HDT did not significantly change femoral arterial pressure when compared before and after HDT (Table 1). These results suggest that exposure to 45° HDT is a useful model with which to investigate the effects of simulated microgravity on ICP in rabbits.

In conclusion, ICP increased at the beginning of 8 h of HDT and decreased toward the pre-HDT baseline value during the next several hours. It is suggested that edema formation plays little role in the mechanism for the initial increase in ICP and that venous engorgement in the brain tissues and the CSF shift from spinal subarachnoid space into the intracranial subarachnoid space seem to be involved in it.

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