EFFECTS OF ALTERED GRAVITY ON CEREBRAL CIRCULATION

重力変化が脳循環に与える影響

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ABSTRACT

Using non-invasive techniques, such as a carotid Doppler flowmeter, a transcranial Doppler sonography, and a near infrared spectrophotometer (NIRS), the author examined the effects of altered gravity on cerebral hemodynamics in healthy human volunteers. Measurement of cerebral hemodynamics was carried out on the following experimental conditions: 1) head-up tilt at 60 degrees for 15 minutes (n=7); 2) 1.5 G centrifugation (head to foot direction) for 30 minutes (n=8); 3) application of 30 mmHg negative pressure to the lower body for 30 minutes (n=7); and 4) parabolic flight on a jet airplane, which produces zero gravity approximately for 25 seconds (n=4). During head-up tilt, blood flow rate at the common carotid artery (FRCCA) and flow velocity at the middle cerebral artery (FVMCA) were significantly decreased, and NIRS showed the significant decrease in the oxygenated hemoglobin in the brain tissue (oxy-Hb) with the slight increase in deoxygenated hemoglobin (deoxy-Hb). During centrifugation, oxy-Hb was significantly decreased with the slight increase of deoxy-Hb. During application of lower body negative pressure (LBNP), both of FRCCA and FVMCA were significantly decreased, and also NIRS revealed the significant increase in oxy-Hb without significant changes in deoxy-Hb. During a zero gravity period produced by parabolic flight, FVMCA was significantly increased, and NIRS showed the significant increase in oxy-Hb. Deoxy-Hb was slightly decreased during a zero gravity period except for one subject. According to a model analysis, the changes in oxy- and deoxy-Hb during the zero gravity period indicate the increase in cerebral blood flow (CBF). Taken together, the results suggest that CBF and cerebral blood volume (CBV) are decreased during exposure to hypergravity and increased during exposure to hypogravity. Furthermore, the fact that LBNP, which does not have hydrostatic pressure effect, decreases CBF probably indicates that, in altered gravitational fields at a range between 0 and 2G, the major affecting factor to the CBF regulation is the change in cardiac output caused by blood shift. In conclusion, CBF and CBV are decreased during exposure to hypergravity, and increased during exposure to hypogravity. CBF cannot be completely maintained in altered gravitational environments at 0 to +2 Gz level.

GLOSSARY OF SYMBOL

ANOVA	analysis of variance
bpm	beat per minute
CDF	carotid Doppler flowmeter
CBF	cerebral blood flow
CBV	cerebral blood volume
$CMRO_2$	cerebral metabolic ratio of oxygen
DBP	diastolic blood pressure
Cyto	cytochrome aa^3
deoxy-	deoxygenated
ECG	electrocardiogram
FRCCA	flow rate at the common carotid artery
FVMCA	flow velocity at the middle cerebral artery
Gx	gravitational force from front to back
Gy	gravitational force perpendicular to a sagittal plane
Gz	gravitational force from head to foot
Hb	hemoglobin
HR	heart rate
KIAS	knots indicated air speed
LBNP	lower body negative pressure
NIRS	near infrared spectrophotometer
oxy-	oxygenated
Recov.	the 6 second-period when the gravity is stable at 1 G level
SaO_2	oxygen saturation of the arterial blood
SvO_2	oxygen saturation of the venous blood
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean

TCD	transcranial Doppler sonography
2G in	6 second-period just after the gravity is rapidly increased from 1G to 2G during a parabolic flight
2G out	6 second-period just before the gravity is rapidly decreased from 2G during a parabolic flight
0G in	6 second-period just after the gravity is rapidly decreased from 2G to 0G during a parabolic flight
0G out	6 second-period just before the gravity is rapidly decreased from 0G during a parabolic flight

CONTENTS

1
INTRODUCTION

As aerospace technologies develop, physiological responses to gravitational stress become a concern to assure human safety. Acceleration force produces hydrostatic pressure gradient in vascular column. Vascular pressure at a specific point therefore becomes dependent on hydrostatic pressure changes caused by a gravitational force. Intravascular pressure (P) can be expressed as

$$P = P_0 - \rho G h$$

where P_0 = intravascular pressure at heart level, ρ = specific density of blood, G = inertial force and h = height of the fluid column (upper: h>0, lower: h<0). Altered intravascular pressure causes various physiologic effect on circulation (Watenpaugh and Hargens, 1996; Burton and Smith, 1996).

Gravitational forces are expressed as Gx (front to back), Gy (perpendicular to a sagittal plane), and Gz (head to foot). According to previous reports (Brinkley and Raddin, 1985; Burton et al., 1985; Leverett and Whinnery; 1985), Gz stress is the most important to determine the human tolerance and response to gravitational stress.

There have been quite a few reports on cardiovascular hemodynamics in altered gravitational environments (Gz direction). During exposure to hypergravity (> +1 Gz), arterial blood pressure at heart level are well maintained or increased with increased heart rate, while cardiac output is decreased (Bartok et al., 1968; Shvartz and Meterstein, 1970). These responses are related to the pooling of the blood in the lower body, which results from the increased venous pressure in the lower body due to the hydrostatic pressure effect. During exposure to hypogravity (< +1 Gz), arterial blood pressure at heart level is also well maintained or slightly decreased, while heart rate is slightly decreased, showing an increase in cardiac output (Mukai

et al., 1991). In the hypogravity environment, blood is released from the lower to the upper body due to the hydrostatic pressure decrease in the lower body.

In order to assure human safety during exposure to altered gravitational stress, it seems important to clarify effects of altered gravity on the cerebrovascular system.

Many researchers in the field of aviation medicine have been interested in cerebral hemodynamics during exposure to hypergravity (Burton, 1985; Burton et al., 1996; Howard et al., 1965; Glaister, 1988; Ossard et al., 1994; Werchan et al., 1991). This is because loss of consciousness which occurs at 3 or 4 Gz level without any anti-gravity maneuvers is a well-known risk on high performance aircraft. CBF might be affected at such high level of hypergravity, as several researchers tentatively suggested (Glaister, 1988; Ossard et al., 1994; Werchan et al., 1991).

From the viewpoint of space medicine, it also seems important to evaluate effects of a lower level (less than 2 Gz) of hypergravity, which seldom induces loss of consciousness in healthy humans, on cerebral hemodynamics. This is because, on returning to the earth on Space Shuttle, astronauts are exposed to a hypergravity environment at 1.2 Gz on the average, maximally 2 Gz, for 17-20 minutes (Nicogossian and Robbins, 1994). Also, effects of hypogravity on cerebral hemodynamics should be important to assure astronauts' performance in space. However, cerebral hemodynamics have rarely been measured in altered gravitational environments, neither hypergravity (less than 2 Gz) nor hypogravity.

The purpose of the present study was therefore to evaluate cerebral hemodynamics in altered gravity environments, especially lower level hypergravity and hypogravity, in humans. By conventional methods such as H_2 clearance method, ^{133}Xenon inhalation or Positron Emission Tomography, measurement of cerebral hemodynamics in humans has been difficult to perform in dynamic gravitational environments. Accordingly, in the present study, cerebral hemodynamics was measured continuously by a combination of non-invasive measurement devices recently developed, such as a carotid Doppler flow meter

(CDF), a transcranial Doppler sonography (TCD) and a near infrared spectrophotometer (NIRS).

Measurement of the physiological responses to gravitational stress has been carried out using several ground-based techniques. Head-up tilt is an easy way to simulate the effects of +Gz stress by changing a person from supine to head-up position (Bartok et al., 1968; Samueloff et al., 1966; Wang et al., 1960). Centrifugation provides actual +Gz stress. Application of lower body negative pressure (LBNP), which reduces circulating blood volume by pooling blood in the lower body (Murray et al., 1967; Raven et al., 1984; Wolthuis et al., 1970), has also been used as a tool for simulating the cardiovascular responses to +Gz stress. On the other hand, parabolic flight is the only unique environment in which human can experience zero gravity on Earth, although weightlessness lasts only for 20-30 seconds (Watenpaugh and Hargens, 1996). In the present study, cerebral hemodynamics are assessed in all of the above four environments.

2
MEASUREMENT INSTRUMENTS

The present study consists of four experimental procedures, and the same measurement instruments were used in each experiment. To avoid redundancy, details of the measurement instruments are described first.

2.1 Carotid Doppler flowmeter (CDF)

The flow rate at the common carotid artery (FRCCA) can be measured with a carotid Doppler flowmeter (QFM-1100, Hadeco Hayashi Denki Corporation, Kawasaki, Japan). The instrument has two features (Furuhata et al., 1978; Uematsu, 1981): 1) the angle-independence between the probe and the vessel; and 2) the calculation of the common carotid blood flow by measuring simultaneously its diameter and the flow velocity. A high correlation ($r = + 0.99$) has been reported between the values measured with the carotid Doppler flowmeter and those measured with the electromagnetic flow meter (Uematsu, 1981).

The principles of the carotid Doppler flowmeter are described in detail elsewhere (Furuhata et al., 1978; Uematsu, 1981). The probe is placed over the common carotid artery with minimum pressure to prevent the arterial compression. An A-mode transducer is used to measure the diameter of the pulsating artery continuously. An operator moves a tracking gate onto the arterial wall in the A-mode echo screen. The tracking gate automatically follows the motion of the arterial wall, and then the diameter of the pulsating artery is calculated every 2 ms from the distance between the two tracking gates.

The two transducers receiving Doppler signals are placed on both sides of the transmitting transducer at a predetermined angle (Fig. 2-1). As shown in the

Appendix A, by placing two receiving transducers, we can obtain the blood flow velocity independently of the angle between the probe and the artery. The flow rate is calculated from the velocity and the diameter measured every 2 ms. Subsequently, the area-averaged blood flow per minute is calculated from the data over 5 cardiac cycles.

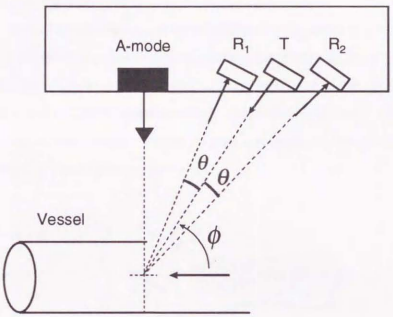


Figure. 2-1 A diagram of the carotid Doppler flowmeter probe. ϕ : the angle between the transmitting Doppler transducer (T) and the direction of blood flow. θ : the fixed predetermined angle between the transmitting (T) and receiving (R_1 and R_2) Doppler transducers. As shown in Appendix, the flow velocity can be calculated independently of the angle ϕ. (modified from Uematsu, 1981)

2.2 Transcranial Doppler sonography (TCD)

The flow velocity of the middle cerebral artery (FVMCA) can be monitored with the transcranial Doppler sonography (Transpect TCD), which was introduced as a high-energy bidirectional pulsed Doppler system operating at lower frequencies (1-

2MHz) (Aaslid et al., 1982). The ultrasound signals at the lower frequencies penetrate the bone sufficiently to reach the intracranial artery. The signals reflected by moving objects (blood cells) can be detected with a 2-MHz probe. The 64-point fast Fourier transformation spectrum analyzer displays the flow velocity spectra continuously, and the area-averaged mean flow velocity is calculated every 4 seconds. The TCD enables us to measure only the flow velocity (i.e. cm/sec), but not the flow rate (i.e. ml/min).

The probe is placed on the temporal bone above the zygomatic arch. The so-called "ultrasonic window" can be found by moving the probe in small steps. The middle cerebral artery is identified by the flow direction (toward the probe) and by the depth from the skin surface (approximately between 40-60 mm), followed by fixing the probe with a head band. The angle and the depth of the probe are maintained throughout each procedure.

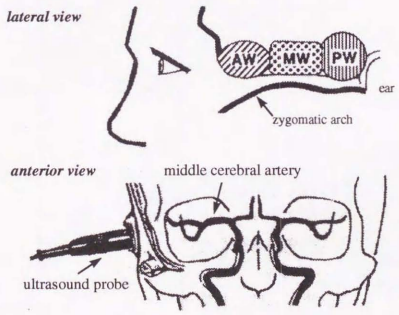


Figure. 2-2 A schema of a transcranial Doppler sonography. The upper shows the so-called ultrasonic windows. AW: anterior window, MW: middle window, PW: posterior window. The bottom shows the relationship between the probe and the artery.

2.3 Near infrared spectrophotometer (NIRS)

The near infrared spectrophotometer (NIRO-500, Hamamatsu Photonics, Hamamatsu, Japan), whose principle was demonstrated by Jobsis (1977a, 1977b), was used to continuously measure the absorption changes of the laser signals reflected by the brain tissue. Changes in the quantity of oxy-Hb and deoxy-Hb within the illuminated brain tissues can be calculated (Jobsis, 1986; Wyatt et al., 1986).

The methodology of this spectrophotometry is detailed elsewhere (Jobsis, 1977a; Jobsis, 1977b; Jobsis, 1986; Wyatt et al., 1986; Edwards et al., 1988).

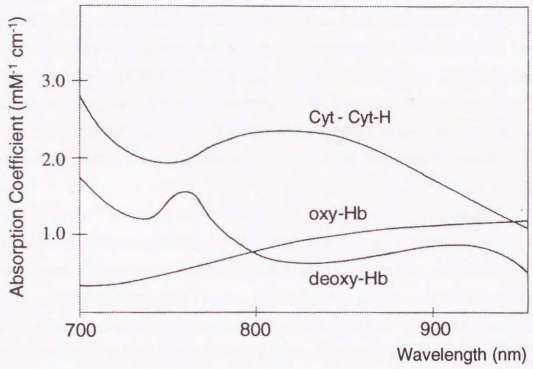


Figure. 2-3 Absorption spectrum of oxy-Hb, deoxy-Hb, and cytochrome aa^3. The value of cytochrome aa^3 is shown as the subtraction between oxygenated (Cyt) and deoxygenated cytochrome aa^3 (Cyt-H).

Briefly, the near infrared light has the following features: (1) the near infrared light penetrates skin and bone much more readily than other wavelengths; (2) hemoglobin and cytochrome aa^3 are the only detectable biological compounds that absorb the near infrared light. The absorption by water can be negligible. Also, the oxygenated and deoxygenated compounds have different absorption spectra from each other, as shown in Fig. 2-3. Accordingly, by utilizing multi-wavelength near infrared light from several laser diodes, changes in the quantity of oxy-, deoxy-Hb and cytochrome aa^3 can be calculated by linear summation of the absorption changes multiplied by the coefficients at each wavelength (Wyatt et al., 1986). The mathematical details are described in Appendix.

The apparatus has two fiber-optic bundles terminating in two optodes placed 35 mm apart, about 30 mm superior to the upper orbital margin on the forehead. They are fixed with sufficient pressure to minimize the skin contribution to the laser signals. Background light is excluded with an opaque cloth. The near infrared light from four laser diodes (778, 813, 867 and 904 nm in wavelength) is directed toward the head by one optode. By the other optode, the light reflected by the brain tissue is collected and it is carried to a photomultiplier operating in a photon counting mode. Changes in the quantity of oxy- and deoxy-Hb are calculated every 2 seconds.

Biological tissue scatters photon traveling in it, and the photon migrates considerably further through the tissue than the direct distance between the two optodes. These distortion and scattering effects of the light are the complications related to the spectrophotometry (Jobsis, 1977b). Although these effects make it difficult to trace the optic pathway, several attempts have been made to reveal the photon migration in biological tissue. Monte Carlo simulation (Arridge et al., 1992; Hiraoka et al., 1993) and experimental measurements (Cui et al., 1991; Gratton et al., 1994) shows that the photon migrates through the optic pathway distributed in a region shaped as a "banana", with its two ends connecting the two optodes and with its mid portion reaching deepest. The optic pathway reaches the depth of 6- 7 cm at maximum and 2-3 cm on the average (Cui et al., 1991). The bone contributes

maximally about 5% to the laser signals (Jobsis, 1977b). Also, Delpy et al. (1988) concluded that the bone and the dura make negligible contribution to the time profile of light by measuring the time-interval traveled through tissue. Accordingly, by placing optodes on the forehead, we can obtain the information about the changes in oxy- and deoxy-Hb quantity in the regional frontal lobe illuminated by near infrared light.

In spite of the above previous attempts, the optic pathway cannot precisely be identified in each subject. Accordingly calculated values are not absolute but are defined by the photoabsorption changes of the reflected near infrared laser within the brain tissues. The unit is arbitrarily nominated.

The values of arterial oxygen saturation are essential to interpret the quantity changes in oxy- and deoxy-Hb. The arterial oxygen saturation was continuously monitored at the thumb with the pulse oximeter (Oxypal OLV-1200, Nihon Kohden Corporation, Tokyo, Japan).

2.4 Statistical analysis

The data were subjected to a repeated-measures analysis of variance (ANOVA) which evaluates statistical differences across the time course, followed by post-hoc comparisons (Scheffe's F test or Fisher LSD). Differences are considered significant at a level of $p<0.05$.

3
HEAD-UP TILT

Tilting a person from supine to head-up position at θ degree can change Gz gravitational force from *0* to *Sin θ* Gz. Accordingly, head-up tilt has been used to assess physiologic responses to orthostatic stress. In the present study, head-up tilt study was designed to investigate effects of altered Gz force (from 0 to Sin 60°) on cerebral hemodynamics.

There are several reports which documented the relationship between tilt angle and cardiovascular response (Tuckman and Shillingford, 1966). Thus, in the present study, relationship between tilt angle and cerebral hemodynamics was also evaluated.

3.1 Procedure

Subjects: We performed two kinds of head-up tilt tests, Head-up tilt I and II. Seven healthy male volunteers, with a mean age of 21 ± 3 years (mean ± SD), a mean height of 170 ± 7 cm and a mean weight of 64 ± 4 kg, participated in the experiment Head-up tilt I. Eight healthy female volunteers, with a mean age of 20 ± 1 years (mean ± SD), a mean height of 160 ± 3 and a mean weight of 50 ± 4 kg, participated in the experiment Head-up tilt II. Each subject passed a physical examination (ECG and chest X-ray) to screen for possible cardiopulmonary diseases. Subjects were fully briefed as to the procedures and the possible risks, and gave their written consent to participate. All the procedures were performed according to the principles set out in the Declaration of Helsinki.

Protocol: In the Head-up tilt I, all seven subjects rested in supine position on a tilt table which could be tilted automatically. After having baseline measurements taken for 30 minutes, we tilted them to a head-up position at 60 degrees in 30 seconds, keeping them in this position for 15 minutes. We also kept taking measurements for another 5 minutes after placing them back to supine position. This procedure was repeated on a separate day for each subject.

In the Head-up tilt II, all eight subjects were tilted to head-up positions of 15, 30, 45, and 60 degrees, separately. Each head-up tilt test was performed in the same manner as described for Head-up tilt I. Each subject was tilted four times, such that a total of 32 head-up tilt tests were done. The order of tilt angles was randomized.

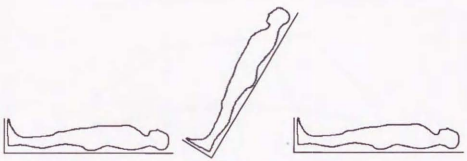


Figure. 3-1 A schema of head-up tilt

Measurements: Systolic and diastolic blood pressure, abbreviated as SBP and DBP respectively, were taken every minute with an electric sphygmomanometer. Heart rate (HR) was recorded every minute with an electrocardiograph.

Flow rate at the common carotid artery (FRCCA) was measured with CDF every 5 minutes. Flow velocity of the middle cerebral artery (FVMCA) and changes in the quantity of oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin in the brain were measured continuously with TCD and the NIRS, respectively.

3.2 Results

Head-up Tilt I

SBP, DBP and HR during exposure to head-up tilt are presented in Fig. 3-2. SBP showed no significant change across the time course ($F(4,44)=1.17$, $p=0.35$). DBP and HR showed significant differences across the time course (DBP:$F(4,44)=11.91$, $p<0.0001$, SBP:$F(4,44)=37.45$, $p<0.0001$). Post-hoc comparisons revealed that DBP and HR were significantly increased throughout head-up tilt.

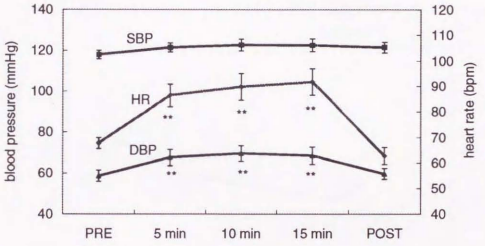


Figure. 3-2 The mean values for SBP, DBP and HR during head-up tilt (n=7). Vertical bars represent SEM. **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt.

FRCCA showed a significant difference across the time course ($F(4,39)=8.40$, $p<0.0001$) (Fig. 3-3). Post-hoc comparisons revealed a significant decrease during head-up tilt.

FVMCA showed a significant difference across the time course ($F(4,29)=8.03$, $p=0.0005$) (Fig. 3-3). Post-hoc comparisons revealed a significant decrease during head-up tilt.

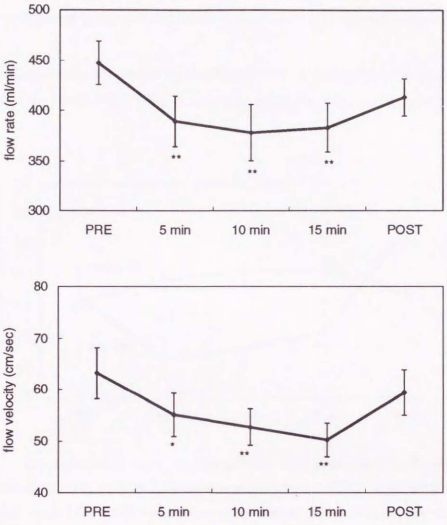


Figure. 3-3 The mean values for flow rate at the common carotid artery (*top*) and flow velocity at the middle cerebral artery (*bottom*) during head-up tilt (n=7). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt.

Oxy-Hb quantity in the brain tissue showed a significant difference across the time course ($F(4,39)=39.50$, $p<0.0001$) (Fig. 3-4). The oxy-Hb in the brain was decreased after starting head-up tilt, and thereafter gradually increased. After

subjects were returned to supine position, it exceeded control levels, and thereafter gradually recovered to the starting level in approximately 10 min (data not shown in Fig. 3-4).

Deoxy-Hb quantity showed a significant difference across the time course ($F(4,39)=21.15$, $p=<0.0001$) (Fig. 3-4). It was gradually increased during head-up tilt.

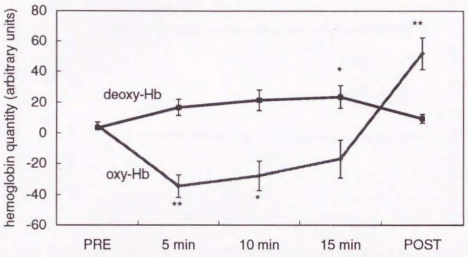


Figure. 3-4 The mean values for oxy-Hb and deoxy-Hb during head-up tilt (n=7). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt. Although the oxy-Hb exceeded control level at POST, the value thereafter gradually recovered to the control level in approximately 10 min.

Head-up Tilt II

SBP and DBP showed no significant changes during head-up tilt (Fig. 3-5). HR showed significant increases at 45 and 60 degrees (vs. pre values, 45 degrees; $F(4,28)=16.56$, $p<0.0001$, 60 degrees; $F(4,28)=10.61$, $p<0.0001$) (Fig. 3-6).

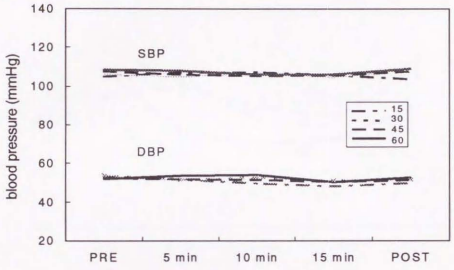


Figure. 3-5 The mean values for SBP and DBP during head-up tilt at 15, 30, 45 and 60 degrees (n=8). PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt.

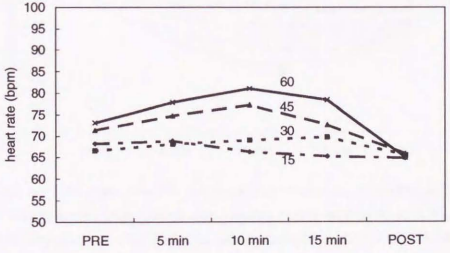


Figure. 3-6 The mean values for HR during head-up tilt at 15, 30, 45 and 60 degrees (n=8). PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt.

FRCCA showed a significant decrease at 60 degrees (vs. pre value, $F(4,28)=10.61$, $p<0.0001$) (Fig. 3-7).

FVMCA was significantly decreased across the time course at 45 and 60 degrees (vs. pre value, 45 degrees: $F(4,20)=7.73$, $p=0.0006$; 60 degrees: $F(4,20)=8.03$, $p=0.0005$) (Fig. 3-7).

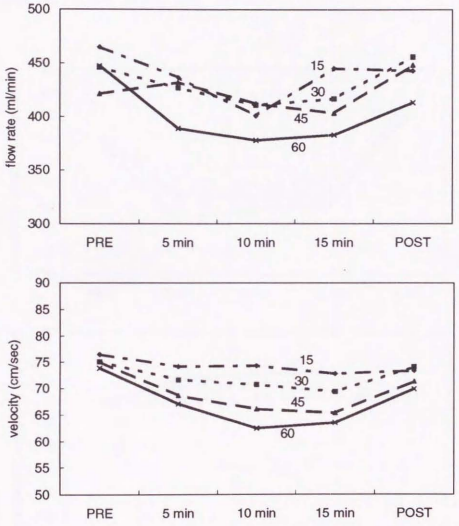


Figure. 3-7 The mean values for flow rate at the common carotid artery (*top*) and flow velocity at the middle cerebral artery (*bottom*) during head-up tilt at 15, 30, 45 and 60 degrees (n=8). PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt.

The oxy-Hb quantity showed significant decreases at all the tilt angles (vs. pre values, 15 degrees; $F(4,28)=14.75$, $p<0.0001$, 30 degrees; $F(4,28)=24.88$, $p<0.0001$, 45 degrees; $F(4,28)=43.50$, $p<0.0001$, 60 degrees; $F(4,28)=39.50$, $p<0.0001$) (Fig. 3-7). The deoxy-Hb quantity showed significant increases at 45 and 60 degrees (vs. pre values, 45 degrees; $F(4,28)=15.77$, $p<0.0001$, 60 degrees; $F(4,28)=21.15$, $p<0.0001$) (Fig. 3-8).

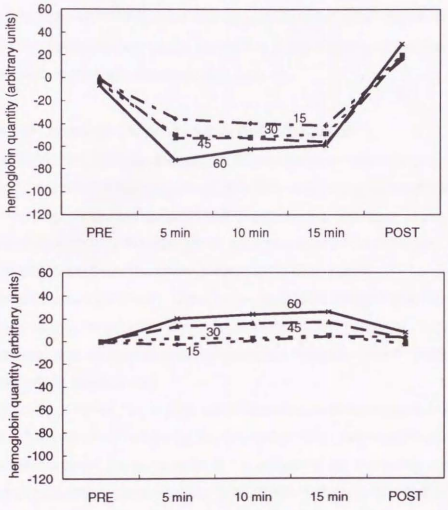


Figure. 3-8 The mean values for the oxy-Hb (*top*) and the deoxy-Hb (*bottom*) during head-up tilt at 15, 30, 45 and 60 degrees (n=8). PRE: 5 minutes before starting head-up tilt, POST: 5 minutes after ceasing head-up tilt.

3.3 Discussion

Head-up tilt is an easy way to simulate the effects of +Gz stress by changing a person form supine to head-up position. Passive tilting, which means that a person is tilted automatically by a table, causes pooling of circulating blood in the lower body, resulting in cardiac output reduction (Bartok et al., 1968; Samueloff et al., 1966; Wang et al., 1960).

A literature review (Kapoor et al., 1994) recommended protocols of passive tilt testing procedures at 60° since the overall specificity is higher with this method. Consequently, in the present study, we set the tilting angle to 60° so as to elicit the cardiovascular responses previously reported.

Effects of 60° Head-up Tilt on Cerebral Hemodynamics

In the results, FRCCA was decreased. Of the common carotid blood flow, 70% is distributed to the internal carotid artery, and 30% is to the external (Kristiansen, 1962). Accordingly it seems quite difficult to explain the decrease in the common carotid blood flow only by the decreased external carotid flow. The internal carotid blood flow, which supplies the brain, seems to be decreased.

FVMCA was also decreased. There is the possibility that the flow velocity was decreased due to a dilation of the middle cerebral artery. However, Larsen et al. (1994) reported that, in normal healthy subjects, changes in the FVMCA are mostly due to changes in the flow rate.

In the results of NIRS, the oxy-Hb was decreased with the slight increase in the deoxy-Hb. This indicates that the oxygen saturation of the venous blood (SvO_2) was decreased in the brain, because most of the deoxy-Hb are in the venous blood. According to previous reports (Powers et al., 1984; Scheinberg, 1949), cerebral metabolic ratio of the oxygen ($CMRO_2$) remains fairly constant during the postural changes. Accordingly, the NIRS results also suggest that CBF, which is expressed as $CBF = CMRO_2 / (1\text{-}SvO_2)$, might be decreased.

CBF was not directly measured in the present study. However, it seems difficult to explain all of the results reasonably without concluding that CBF was decreased. Also, NIRS suggests that CBV (total hemoglobin quantity) was decreased during a head-up tilt.

During head-up tilt, the arterial intravascular pressure at the head level is decreased due to the hydrostatic pressure effect (Watenpaugh and Hargens, 1996). According to previous reports (Fog, 1949; Heistad and Kontos, 1983; Scheinberg, 1949), the decrease in the arterial intravascular pressure in the brain causes the decrease in the vascular tonus, resulting in autoregulatory vasodilatation. Although the results cannot lead us to a definite conclusion, the increased oxy-Hb observed during the 5th to the 15th minutes of a head-up tilt might be related to the arterial vasodilatation. Also, the overshooting increase in the oxy-Hb after ceasing a head-up tilt can be explained by the decreased vascular tonus.

Several trials were previously conducted to measure CBF in normal healthy subjects using the ^{133}Xenon inhalation method and the nitric oxide method. Some of them (Brooks et al., 1989; Shenkin et al., 1950) demonstrated no changes in CBF, which seemingly differ from the present study. On the contrary, Scheinberg et al. (1949) reported a decrease in CBF during head-up tilt using the nitric oxide method. The ^{133}Xenon inhalation method and the nitric oxide method provide no continuous data. Additionally, it is possible that inhalation affects CBF regulation. These might be the reasons for the contradictory results. In the present study, measurements were made continuously and non-invasively.

Also, a few attempts were recently reported to measure the flow velocity at the middle cerebral artery during head-up tilt, showing the decrease in the flow velocity (Leftheriotis et al., 1992; Jorgensen et al., 1993). However, in these studies, the mean arterial pressure was decreased or the subjects had the endpoint due to pre-syncopal status. Accordingly, it is difficult to conclude that their results represent the responses of healthy humans.

In the present study, the cardiovascular responses are consistent with those of previous reports where none of the subjects had presyncope during head-up tilt.

Consequently, the present study may be the first report providing continuous data on cerebral hemodynamics during exposure to head-up tilt in normal healthy humans.

Relationship between Tilt Angle and Cerebral Hemodynamics

Previous report documented that cardiac output was decreased 5%, 17%, 19% and 19% at 10°, 20°, 30° and 60°, respectively (Tuckman and Shillingford, 1966). In the present results, cerebrovascular responses to head-up tilt is also dependent on tilt angle.

During head-up tilt at 45 and 60 degrees, FVMCA was decreased, and the oxy-Hb showed a decrease with a slight increase in the deoxy-Hb, as observed in the Head-up tilt I. These results suggest that CBF and CBV were decreased at 45 and 60 degrees.

At 15 and 30 degrees, the oxy-Hb quantity was decreased, but the deoxy-Hb quantity showed no significant change. Thus, in the results of NIRS, SvO_2 in the brain might be decreased, suggesting that CBF was slightly decreased. However, FRCCA and FVMCA showed no significant changes. Accordingly, at 15 and 30 degrees, CBF might show no significant change or a slight decrease, if any.

Taken together, CBV was decreased at 15°, 30°, 45° and 60°, while CBF showed a significant decrease at 45° and 60°.

3.4 Summary

CBF and CBV are both decreased during 60° head-up tilt (Gz change is from 0 to 0.87 Gz). CBF decrease seems dependent on tilt angle, while the magnitude of CBV decrease is almost the same at each tilt angle. Possible mechanisms to explain this result will be discussed in the Chapter 7.

4
CENTRIFUGATION

Although a head-up tilt alters Gz force from 0 to maximally 1 Gz (upright), centrifugation can produce artificial hypergravity (> 1Gz). As already mentioned, the overall purpose of the present study is to evaluate effects of altered gravity, low level hypergravity less than 2 Gz and hypogravity, on cerebral hemodynamics. Accordingly, a centrifugation study was designed to investigate effects of exposure to 1.5 Gz on cerebral hemodynamics. From the viewpoint of space medicine, the duration of exposure to 1.5 Gz was set to 30 min because, on returning to Earth on Space Shuttle, astronauts are exposed to hypergravity at 1.2 Gz on the average, maximally 2 Gz, for 17-20 min.

4.1 Procedure

Subjects: Eight female subjects, with a mean age of 20 ± 1, a mean height of 160 ± 5 cm and a mean weight of 50 ± 5 kg, were studied. All subjects had a negative history of cardiopulmonary diseases with a normal ECG and a normal chest X-ray. Subjects were fully briefed as to the procedures and the possible risks, and gave their written consent to participate. All the procedures were performed according to the principles set out in the Declaration of Helsinki.

Protocol: Acceleration was provided by a short arm centrifuge system which was manufactured by Daiichi Ika Co. Ltd, Tokyo, Japan in collaboration with the Department of Hygiene, Nihon University School of Medicine. This device, with a radius of 2.4m, can produce a maximum of 3.0 G artificial gravity from head to foot. In the present study, a subject was exposed to 1.5 Gz with an onset rate of 0.01 G/sec. The plateau gravity level was maintained for 30 minutes. An offset rate was 0.01 G/sec.

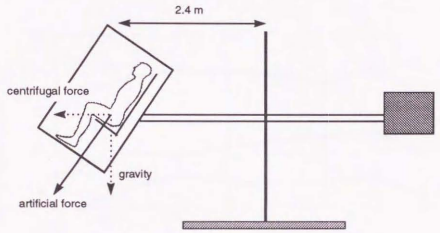


Figure. 4-1 A schema of a short-arm centrifuge system

Measurements: SBP and DBP were recorded every minute with an automatic sphygmomanometer. HR was monitored with an electrocardiogram.

Changes in the oxy-Hb and deoxy-Hb quantity in the brain were measured continuously with NIRS. FRCCA and FVMCA were not measured because of technical limitations.

4.2 Results

SBP, DBP and HR during centrifugation are presented in Fig. 4-2. SBP, DBP and HR showed significant changes across the time course (SBP:F(8,53)=4.39, p=0.0007, DBP:F(8,53)=2.78, p=0.015, HR:F(8,53)=4.30, p=0.0008). Post-hoc comparisons revealed significant increases in SBP, DBP and HR during 30 min of 1.5 Gz centrifugation.

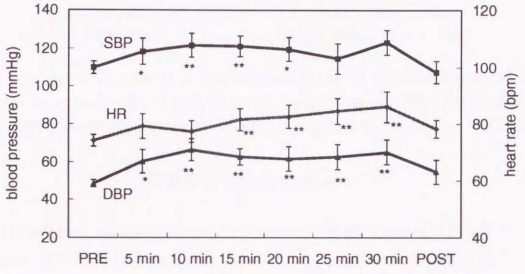


Figure. 4-2 The mean values for SBP, DBP and HR during 1.5 Gz centrifugation (n=8). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before starting centrifugation, POST: 5 minutes after ceasing centrifugation.

The oxy-Hb quantity showed a significant difference across the time course (F(7,31)=2.59, p=0.043) (Fig. 4-3). Post-hoc comparisons revealed a significant decrease at 15 and 30 min of centrifugation. After ceasing centrifugation, the oxy-Hb returned to the starting level. The deoxy-Hb showed no significant change during centrifugation (F(7,31)=2.12, p=0.087) (Fig. 4-3).

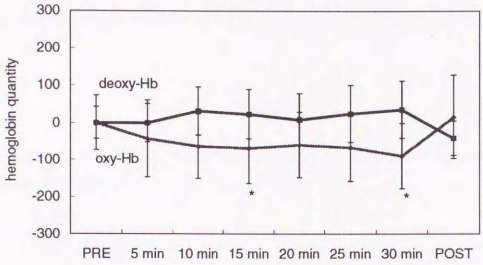


Figure. 4-3 The mean values for oxy-Hb and deoxy-Hb during 1.5 Gz centrifugation (n=8). Vertical bars represent SEM. *p<0.05 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before starting the centrifugation, POST: 5 minutes after ceasing the centrifugation.

4.3 Discussion

The changes in the hemoglobin quantity during 1.5 Gz centrifugation are consistent with those of head-up tilt. Oxy-Hb was decreased while deoxy-Hb showed a slight increase. Thus, the results suggest that CBF and CBV were decreased during 1.5 Gz centrifugation.

Effects of respiratory change during exposure to hypergravity on the results should be addressed. Several studies documented that there is a progressive failure of O2 intake in the lung during exposure to hypergravity due to redistribution of the pulmonary blood flow (Bryan et al., 1965; Burton et al., 1974; Burton and Smith, 1996), while arterial CO_2 pressure is well maintained even at the level of more than 3 Gz. In the present study, arterial O_2 saturation was not changed during centrifugation. We may neglect effects of blood gas change on cerebral hemodynamics during 1.5 Gz centrifugation.

This is the first report to reveal that the sustained exposure to the 1.5 Gz hypergravity decreases the CBF and CBV, while loss of consciousness is not induced.

4.4 Summary

Exposure to 1.5 Gz hypergravity decreases CBF and CBV, which are stabilized at lower level for 30 min.

5
LOWER BODY NEGATIVE PRESSURE

Exposure to +Gz force produces the pooling of the blood in the lower body, resulting in the reduction of cardiac output, and also produces a hydrostatic pressure gradient between the heart and the head level.

Head-up tilt and centrifugation have the both effects (Bartok et al., 1968; Shvartz and Meterstein, 1970). Application of lower body negative pressure (LBNP), however, causes pooling of the blood in the lower body (Musgrave et al., 1969; Stevens and Lamb, 1965; Tripathi and Nadel, 1986) without changing hydrostatic pressure gradient between the heart and head level. Accordingly, we may expect that application of LBNP isolates effects of the blood pooling from the overall effects of exposure to +Gz force.

5.1 Procedure

Subjects: Seven healthy male volunteers, with a mean age of 21 ± 3 years (mean ± SD), a mean height of 170 ± 7 cm and a mean weight of 64 ± 4 kg, participated. Each subject passed a physical examination (ECG and chest X-ray) to screen for possible cardiopulmonary diseases. Subjects were fully briefed as to the procedures and the possible risks, and gave their written consent to participate. All the procedures were performed according to the principles set out in the Declaration of Helsinki.

Protocol: The subjects were reclined in supine position and were enclosed in a box sealed at the level of the anterosuperior iliac crests (Fig. 5-1). Their body was supported with a foot plate. The pressure within the box was reduced below the atmospheric pressure by a vacuum device. Baseline measurements were taken for

30 minutes prior to the LBNP application. LBNP was applied at -10 mmHg for 2 minutes and at -20 mmHg for 3 minutes. The pressure was then decreased to -30 mmHg, and maintained for 25 minutes. Measurements were continued for 5 minutes after ceasing LBNP application.

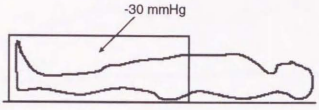


Figure. 5-1 Application of lower body negative pressure

Measurements: SBP and DBP were taken every minute with an electric sphygmomanometer. HR was recorded every minute with an electrocardiograph.

FRCCA was measured with the CDF every 5 minutes. FVMCA and changes in the oxy-Hb and deoxy-Hb quantity in the brain were measured continuously with TCD and NIRS, respectively.

5.2 Results

SBP and DBP revealed no significant differences during 30 mmHg LBNP (SBP:$F(7,55)=3.03$, $p=0.11$, DBP:$F(7,55)=1.32$, $p=0.26$) (Fig. 5-2). HR showed a significant difference across the time course ($F(7,55)=3.86$, $p=0.0025$) (Fig. 5-2). Post-hoc comparisons revealed a significant increase during the LBNP application.

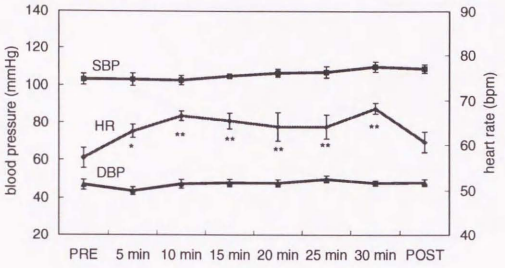


Figure. 5-2 The mean values for SBP, DBP and HR during 30 mmHg LBNP (n=7). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before applying lower body negative pressure, POST: 5 minutes after ceasing lower body negative pressure.

FRCCA and FVMCA showed a significant difference across the time course (CA:$F(2,11)=14.57$, $p=0.005$, MCA:$F(7,55)=3.17$, $p=0.0088$) (Fig. 5-3). Post-hoc comparisons revealed significant decreases during LBNP.

The oxy-Hb quantity showed a significant difference across the time course ($F(7,63)=10.75$, $p<0.0001$) (Fig. 5-4). Post-hoc comparisons revealed a significant increase during LBNP. The deoxy-Hb quantity showed a significant difference across the time course ($F(7,63)=2.80$, $p=0.0155$) (Fig. 5-4). Post-hoc comparisons revealed a significant decrease after ceasing the LBNP application, while there was no significant change during LBNP. After ceasing the LBNP application, the oxy- and deoxy-Hb showed overshoot, and thereafter both of them gradually returned to the starting level in approximately 10 min.

Arterial oxygen saturation was maintained constant between 96% and 99% in each subject throughout the procedure.

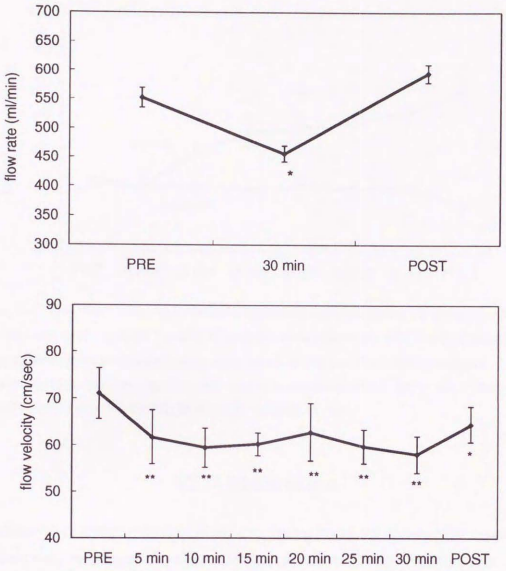


Figure. 5-3 The mean values for flow rate at the common carotid artery (*top*) and flow velocity at the middle cerebral artery (*bottom*) during 30 mmHg LBNP (n=7). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before applying LBNP, POST: 5 minutes after ceasing LBNP.

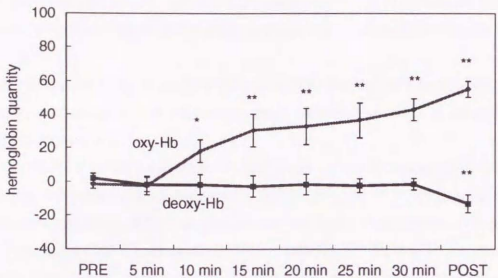


Figure. 5-4 The mean values for oxy-Hb and deoxy-Hb during 30 mmHg LBNP (n=7). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE) PRE: 5 minutes before applying lower body negative pressure, POST: 5 minutes after ceasing negative pressure. Although the oxy- and deoxy-Hb showed overshoot at POST, the values thereafter gradually recovered to the starting level in approximately 10 min.

5.3 Discussion

Application of LBNP reduces central circulating blood volume by pooling blood in the lower body (Murray et al., 1967; Stevens and Lamb, 1965; Wolthuis et al., 1975). LBNP application may be used accordingly as a tool for simulating the hemodynamic responses observed in the standing position (Gilbert et al., 1966; Musgrave et al., 1969), and it can also be used to assess orthostatic intolerance (Murray et al., 1967; Raven et al., 1984; Wolthuis et al., 1970). Previous investigations have demonstrated that even a moderate level of LBNP (30 or 40 mmHg), which does not usually induce syncope in normal healthy adults (Lightfoot, 1991), produces a reduction in central circulating blood volume, and decreases cardiac output (Musgrave et al., 1969; Stevens and Lamb, 1965; Tripathi and Nadel, 1986). At these levels of LBNP, blood pressure is well maintained with

compensatory responses (i.e., the increase in heart rate or in total peripheral resistance). Accordingly, in the present study, the level of LBNP was set to -30 mmHg.

In the results, FRCCA and FVMCA were both decreased during LBNP. As in the results of head-up tilt, we can explain reasonably these results by concluding that CBF is decreased.

The NIRS showed a significant increase in the oxy-Hb during LBNP, but no change in the deoxy-Hb. If we assume that the increased oxy-Hb came from the venous blood, SvO_2 should be increased in the brain. This means an increase in CBF because CBF is expressed as $CBF = CMRO_2 / (1-SvO_2)$. This conclusion is not consistent with the results of CDF and TCD. Consequently, the increased oxy-Hb probably comes from the arterial blood, suggesting that vasodilatation occurred on the arterial side of the brain. After ceasing the LBNP application, the oxy-Hb was increased further without much change in deoxy-Hb. This might be explained by still further vasodilatation on the arterial side of the brain due to decreased vascular tonus.

Fog (1937) reported that the pial arteries dilate following the blood removal, and studies on patients with carotid occlusion (Gibbs, 1984; Powers, 1984), performed by positron emission tomography, showed the increased CBV in the region where the blood flow decreased. These reports support the speculation that autoregulatory vasodilatation might occur during the LBNP application.

Another possible explanation for arterial vasodilatation during LBNP is that an altered arterial CO_2 pressure caused vasodilatation. Arterial CO_2 have a profound relaxant effect on cerebral vascular muscle (Heistad and Kontos, 1983). There is a report that application of LBNP reduces minute ventilation at the level of 40 or 60 mmHg, resulting in the increase of arterial CO_2 pressure (Ahn et al., 1989). In the report, no significant change was observed at the level of 20 mmHg. Accordingly, effects of 30 mmHg LBNP on arterial CO_2 seems unclear from the previous report. In the present study, however, respiration rates showed no significant change during the application of 30 mmHg LBNP (data not shown). It is tentatively

concluded that arterial CO_2 pressure did not playe a predominant role on arterial vasodilatation during 30 mmHg LBNP.

Also, effects of hemoconcentration during exposure to LBNP should be taken into consideration. Extended exposure to LBNP produces loss of plasma volume, resulting in hematocrit increase (Aratow et el., 1993). However, increase in hematocrit cannot explain the oxy-Hb increase without any change in deoxy-Hb. The increased oxy-Hb observed in the present study probably suggests a substantial increase in blood volume.

There are a few reports of decreased blood volume in the head and scalp during LBNP (Savilov, 1992; Wolthuis, 1975), which seemingly differ from the present results. However, this difference may be because the magnitude of their LBNP was -40 or -50 mmHg, or because their measurement included the scalp.

5.4 Summary

Exposure to 30 mmHg LBNP decreases CBF with resulting vasodilatation in the brain, although arterial blood pressure is well maintained.

6
PARABOLIC FLIGHT

Several experimental methods such as head-down tilt or water immersion have been used to simulate the cardiovascular responses in weightlessness environment (Watenpaugh and Hargens, 1996). However, it is unknown whether we may consider the effects of head-down tilt or water immersion on cerebral hemodynamics are also similar to those in space or not. Parabolic flight is therefore the only unique environment in which humans can experience weightlessness on the earth, although weightlessness lasts only for 20-30 seconds and hypergravity (2 Gz at maximum) is imposed during initiation and termination of the parabolic flight.

6.1 Procedure

Subjects: Four healthy volunteers (two male, two female) participated. Each subject passed a physical examination (ECG and chest X-ray) to screen for possible cardiopulmonary diseases. Subjects were fully briefed as to the procedures and the possible risks, and gave their written consent to participate. All the procedures were performed according to the principles set out in the Declaration of Helsinki.

Protocol: The experiments were performed on a jet airplane (MU-300, Diamond Air Service, Nagoya). The trajectory of the MU-300 is presented in Fig. 6-1 with a profile of Gz changes in Fig. 6-2. As shown in Fig. 6-1, the MU-300 parabolic flight is divided into five phases: 1) 1 G phase (horizontal flight), 2) 2 Gz acceleration phase (pull-up, maximally 2.3G), 3) microgravity phase (0.01G), 4) 1.5 Gz acceleration phase (maximally 1.5 G) and 5) 1 G phase (horizontal flight). One parabolic flight is completed for approximately 90 seconds.

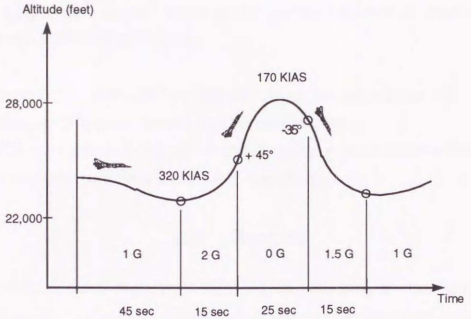


Figure. 6-1 Parabolic flight pattern performed by MU-300. Typical data of the gravity changes are shown in Fig. 6-2. KIAS: knots indicated air speed

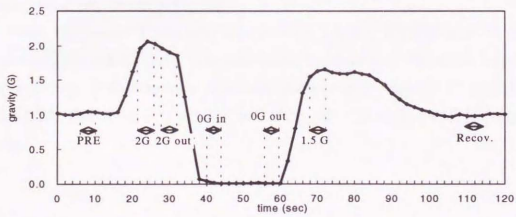


Figure. 6-2 A typical Gz profile in a parabolic flight. Each period is defined as follows; 2 G in: 6 second-period just after the gravity is rapidly increased from 1 G to 2 G. 2 G out: 6 second-period just before the gravity is rapidly decreased from 2G to 0G. 0G in: 6 second-period just after the gravity is rapidly decreased from 2 G to 0 G during a parabolic flight. 0G out: 6 second-period just before the gravity is rapidly decreased from 0 G during a parabolic flight. 1.5 G: 6 second-period just after the gravity is rapidly increased from 0 G to 1.5 G. Recov: 6 second-period when the gravity is stable at 1 G level.

The subjects were seated. The parabolic flight was repeated six times in each subject with a 5-10 minutes interval.

Measurements: SBP, DBP and HR were measured with a finger cuff plesthymogram (Finapres, Omeda Co.Ltd.) beat by beat.

FVMCA and changes in the oxy-Hb and deoxy-Hb in the brain were measured continuously with the TCD and the NIRS, respectively.

6.2 Results

The time courses of all parabolic flights do not completely coincide with each other. Accordingly, the author divided each parabolic flight into seven periods for statistical analysis based upon the onset of rapid gravity-changes: 1) PRE; 2) 2 G in; 2) 2 G out; 3) 0 G in; 4) 0 G out; 5) 1.5 G; 6) Recov. Each period is a 6 second-period. A typical G profile in a parabolic flight and how seven periods are determined are shown in Fig 6-2.

SBP, DBP and HR data are presented in Fig. 6-3. SBP, DBP and HR was gradually increased during 2 Gz-acceleration, showing a peak at the entry to microgravity, while they were decreased during microgravity (SBP:$F(6,118)=4.07$, $p=0.0011$, DBP: $F(6,111) = 3.705$, $p=0.0025$, HR: $F(6,125)=2.515$, $p=0.026$) (Fig. 6-3).

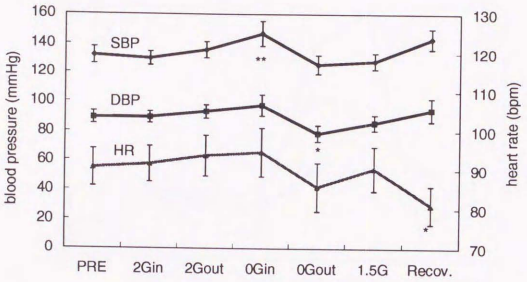


Figure. 6-3 The mean values for SBP, DBP and HR during parabolic flight (n=3, data in one subject were missing due to technical errors). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE)

Individual data for the changes in the oxy- and deoxy-Hb quantity are shown in Fig. 6-4. By visual inspection, the deoxy-Hb changes in one subject are not consistent with those of the other subjects. In this subject, cerebral hemodynamics during parabolic flight seems to be different from others. Accordingly the author analyzed the data of this subject separately.

Mean values for the FVMCA are shown in Fig. 6-5. The flow velocity showed significant differences across the time course ($F(6,153)=18.27$, $p<0.0001$). The flow velocity showed a decrease during the 2G-in period. Post-hoc comparisons revealed a significant increase during the 0G-in period. After exposure to microgravity, the flow velocity recovered to the starting level following a decrease during the 1.5G period.

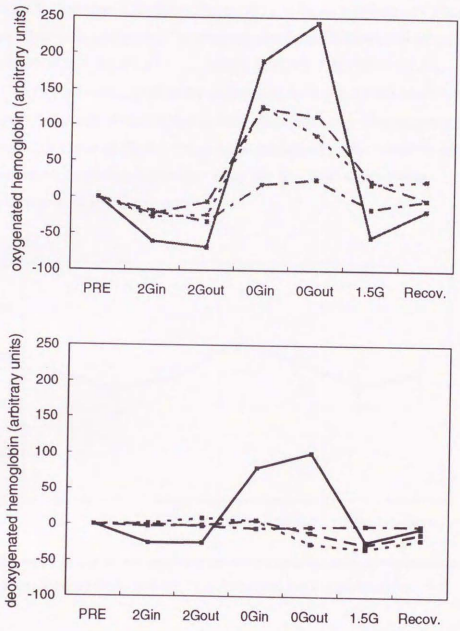


Figure. 6-4 Individual data of hemoglobin quantity in the brain during parabolic flight (n=4). The broken lines represent the data of three Japanese subjects, and the solid line represents the data of an East Indian subject.

Mean values for the oxy- and deoxy-Hb quantity in three subjects are shown in Fig. 6-6 (top) . The oxy- and deoxy-Hb showed significant differences across the time course (OXY:F(6,118)=51.47, $p<0.0001$, DEOXY:F(6,118)=19.555, $p<0.0001$). The oxy-Hb was significantly decreased during 2 Gz acceleration and increased upon the onset of microgravity. After showing a slight decrease at 0G-out (compared with the value at 0G-in), the oxy-Hb recovered to the baseline level. The deoxy-Hb showed no significant changes from pre to 0 G-in while it was significantly decreased at 0 G-out and 1.5 G.

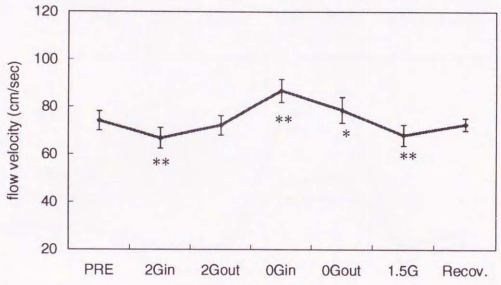


Figure. 6-5 The mean values for flow velocity at the middle cerebral artery during parabolic flight (n=3). Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE)

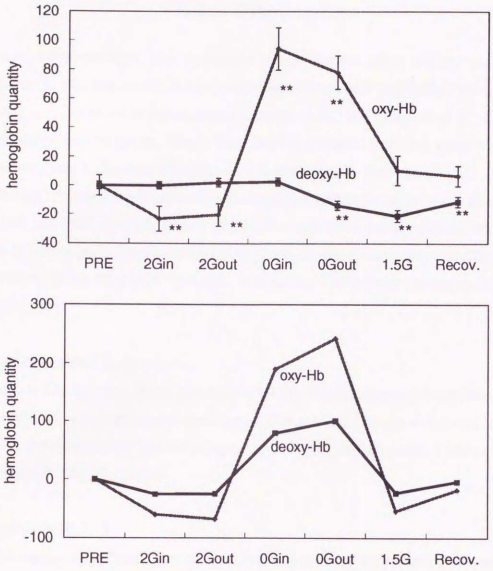


Figure. 6-6 The mean values for oxy-Hb and deoxy-Hb during parabolic flight. The top shows the data of three Japanese subjects, and the bottom shows the data of one East Indian subject. Vertical bars represent SEM. *p<0.05, **p<0.01 by post-hoc comparisons (vs. PRE)

6.3 Discussion

During parabolic flight, blood pressure is well maintained or slightly decreased compared to that measured in horizontal flight. Heart rate is slightly decreased, showing an increase in cardiac output (Bondar et al., 1991; Mukai et al., 1991; Watenpaugh and Hargens, 1996). The blood is released from the lower to the upper body due to the hydrostatic pressure decrease in the lower body.

Although cerebral hemodynamics during parabolic flight have rarely been reported, the present study demonstrated that exposure to hypogravity affected cerebral hemodynamics. Because hypergravity is imposed during initiation and termination of the parabolic flight, the cerebral hemodynamics during each period are discussed.

2 Gz acceleration phase

The oxy-Hb was significantly decreased while the deoxy-Hb showed little change. Also, FVMCA was significantly decreased. Since these results are consistent with those of the head-up tilt and centrifuge experiment, CBF and CBV were probably decreased during this period.

Hypogravity (0.01G)

CBV rapidly increased upon entering into the microgravity. Also, CBF, which is expressed as $CBF = CMRO_2 / (1-SvO_2)$, might be increased during this period because the oxy-Hb increase with the slight decrease in the deoxy-Hb (Fig. 6-6, top) indicates the increase in SvO_2. The increase in the FVMCA supports this speculation.

1.5 Gz acceleration

CBV was decreased compared with that of pre-parabolic flight. The oxy-Hb returned to the starting level while the deoxy-Hb remained still decreased during this period (Fig. 6-6, top). Thus, the SvO_2 in the brain was seemingly increased,

suggesting that CBF was increased compared with that of pre-flight. However, the flow velocity at the middle cerebral artery showed no significant difference compared with that of pre-flight. The changes in CBF during this period might be little. The effects of microgravity on the circulatory system may have persisted during the 1.5 Gz period and canceled the effects of hypergravity.

The above speculation is made in the results of three Japanese subjects (Fig. 6-6, top). In the East Indian subject who showed the different pattern of the deoxy-Hb (Fig. 6-6, bottom), the CBV changes were consistent with those of the three Japanese subjects. However, in this subject, the changes in SvO_2 is not so clear because the oxy- and the deoxy-Hb changes showed the same trend across the time course. Thus, the NIRS data are analyzed by a mathematical model so as to estimate the changes in CBF. The model structure is described in the appendix. The results of three Japanese subjects, presented in Fig. 6-7, top, are consistent with the above speculation. In the results of the East Indian subject (Fig. 6-7, bottom), the arterial blood flow showed the same trend as observed in the other three subjects. Accordingly, as for the effects of parabolic flight on CBF, we may conclude that, in all of the four subjects, CBF was decreased during the acceleration period and increased during the microgravity period.

The difference between the results of the Japanese and the Indian subject is in the changes of the venous drainage on the onset of each gravitational period (2G in, 0G in and 1.5G). In the East Indian subject, the venous drainage was rapidly increased on the onset of the 2 Gz-acceleration, and rapidly decreased after entering into the microgravity period. It is not determined whether this difference comes from a racial or an individual difference.

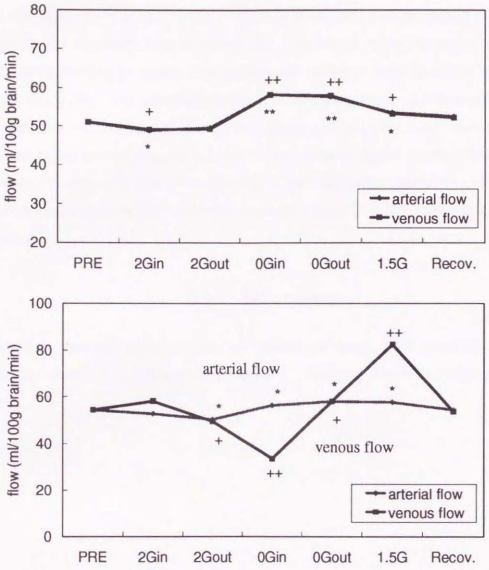


Figure. 6-7 The results of the model analysis for the NIRS data. The top figure shows the changes in the arterial and venous flow in three Japanese subjects. Arterial and venous flow in the top are superimposed on each other. The bottom shows the those in one Indian subject. The model structures are described in the appendix. *p<0.05, **p<0.01 for arterial flow and +p<0.05, ++p<0.01 for venous flow by post-hoc comparisons (vs. PRE)

Previously there was a report to show an increase in the FVMCA during parabolic flight (Bondar et al., 1991), which is consistent with the result of the present study. However, they measured the flow velocity only. During initiation of parabolic flight, CBV is rapidly changed as well as the gravity, as shown in the present study (Fig. 6-6). Accordingly the relationship between the flow velocity (cm/sec) and rate (ml/sec), that is CBF, is unclear in such condition because the diameter of the arterial vessels in the brain might be changed. In the present study, therefore, the oxy- and deoxy-Hb quantity in the brain tissue were measured simultaneously and the CBF changes were estimated from the mathematical analysis.

6.4 Summary

Although there are some differences between subjects, CBF and CBV was decreased during the acceleration period and increased during the microgravity period.

7
EFFECTS OF ALTERED GRAVITY ON CEREBRAL CIRCULATION

The present study revealed that exposure to altered gravity, even at the range between 0 to +2 Gz, affects cerebral circulation. In this chapter, mechanisms of how altered gravity affects cerebral hemodynamics is discussed.

Effects of Hypergravity on Cerebral Circulation

In the results of head-up tilt, centrifugation and parabolic flight (acceleration period), CBV was decreased during exposure to hypergravity. CBV decrease can be explained by venous pressure decrease at head level due to hydrostatic pressure effect. Venous system serves as a blood reservoir because the wall of veins is very distensible. Thus, decrease in cerebral venous pressure can easily decrease CBV. This mechanism also explains why CBV decrease was not observed during LBNP application, which does not produce hydrostatic pressure gradient.

Interestingly, CBV decrease observed in head-up tilt is not so dependent on tilt angle. This might be due to collapse of the neck veins. The veins inside the skull are in a non-collapsible chamber, and they will not collapse. However, the neck veins collapse almost completely all the way to the skull owing to atmospheric pressure in these veins to remain zero along their entire extent (Guyton, 1991). Accordingly, relationship between tilt angle and cerebral venous pressure probably becomes non-linear.

The results also showed that exposure to hypergravity decreased CBF. What mechanisms made CBF decreased during exposure to hypergravity ? There are two possible factors to affect CBF: one is a reduction in cardiac output, and the

other is decrease in perfusion pressure, defined as the difference between arterial and venous pressure, at head level.

Exposure to head-up tilt (Bartok et al., 1968; Samueloff et al., 1966; Wang et al., 1960), centrifugation (Howard, 1965; Bjurstedt et al., 1974) and LBNP (Bartok et al., 1968; Musgrave et al., 1969; Stevens and Lamb, 1965) all causes pooling of circulating blood in the lower body, resulting in a reduction of cardiac filling pressure and cardiac output. In contrast with head-up tilt and centrifugation, however, application of LBNP produces no hydrostatic pressure gradient. Accordingly, it is suggested that cardiac output has a predominant role in CBF decrease during exposure to hypergravity.

Additionally, altered arterial and venous pressure at head level probably affect CBF during exposure to hypergravity. Arterial and venous pressure at head level should be decreased during exposure to hypergravity. However, the magnitude of venous pressure decrease is probably less than that of arterial pressure because the neck veins collapse almost completely all the way to the skull (Guyton, 1991). Negative pressure can exist in the dural sinuses of the head because they are non-collapsible (Rushmer et al., 1947; Guyton, 1991). However, this negative pressure might be insufficient so as to completely compensate arterial pressure decrease at head level.

The results of head-up tilt and LBNP also suggest that arterial vasodilatation occurred in the brain. This vasodilatation might result from autoregulatory responses to decreased CBF during exposure to hypergravity. As previously reported (Heistad and Kontos, 1983), cerebrovascular system actively adjusts vascular muscle activity so as to maintain CBF.

Effects of Hypogravity on Cerebral Circulation

The result of parabolic flight suggests that CBV was increased during exposure to zero gravity. This also can be explained by hydrostatic pressure effect on the cerebral venous system. Exposure to hypogravity should increase venous pressure

at head level due to loss of hydrostatic pressure gradient because anatomically the veins at the neck has no valve as those of the legs do.

As discussed in the Chapter of Parabolic Flight, CBF was increased during short period (approximately 25 sec) of zero gravity. Probably, the CBF increase is also closely related to increase in cardiac output. Mukai and her colleagues (1991) reported that cardiac output was increased in 500 ml/min during exposure to zero gravity.

Relevant problems in the present study

It is noted that the gravity changes produced by each procedure are not uniform with regard to magnitude and duration. Also, posture was not uniform among treatments. During head-up tilt, the +Gz force is changed form 0 to 0.87 (= sin 60°) Gz, and it is maintained for 15 minutes in standing posture. During centrifugation, it is changed from 1 to 1.5 Gz, and it is maintained for 30 minutes in seated posture. During the acceleration period of parabolic flight, the Gz force is changed from 1 to 2 Gz or 0 to 1.5 Gz, and it is maintained approximately for 20 seconds in seated posture. In spite of such variability, CBF and CBV were uniformly affected by altered +Gz force. Consequently, we may conclude that exposure to altered +Gz force, even at 0 to 2 Gz level, affects cerebral hemodynamics. On the other hand, the measurement in hypogravity environment can be made only for 20 seconds. This observation time is too short to investigate compensatory vascular responses. This is the limitation of ground-based experiment with regard to hypogravity. Further study will be necessary during space flight to obtain conclusive data.

Also, each apparatus utilized in the present study has several limitations. By the TCD, only the flow velocity of an intracranial artery is measured. NIRS provides the changes in the hemoglobin quantity only in the regional brain tissue illuminated by near infrared light. However, the simultaneous application of these recently developed methods made it possible to provide continuous information on cerebral hemodynamics in a physiological condition. This seems to be a great advantage, which has never been obtained by conventional methods.

8
CONCLUSION

The present study may be the first report suggesting that CBF cannot be maintained completely in altered gravitational fields with a range of 0 Gz to +2 Gz even though a vascular response, which might be related to autoregulation, occurs on the arterial side of the brain. Also, no data were previously reported concerning CBV changes in dynamic gravitational environments. Measurement of cerebral hemodynamics has been difficult to perform in the dynamic gravitational environments by conventional measurement methods. It can be said that the lack of a non-invasive method to continuously measure CBF and CBV, to date, has precluded the evaluation of cerebral hemodynamics in a physiological condition during exposure to altered gravitational environments.

In conclusion, CBF and CBV decrease during exposure to Gz hypergravity, and increase during exposure to hypogravity. CBF cannot be completely maintained in acutely altered gravitational environments between 0 and +2 Gz, although a compensatory response probably occurs on the arterial side of the brain.

ACKNOWLEDGMENT

The author gratefully acknowledges the enthusiastic participation of our subjects, and also thanks Mr. Toshinaga Kazama, Ms. Ako Aoki and Ms. Yoko Yamada for their engineering efforts and Dr. Satonobu Yoshimoto for helpful discussions.

The experiments of Head-up tilt, Centrifugation, and Lower body negative pressure were made in collaboration with Department of Hygiene, Nihon University School of Medicine, and National Space Development Agency of Japan (NASDA). The experiment of Parabolic flight was conducted in collaboration with Institute of Environmental Medicine, Nagoya University, and NASDA. The author thanks all of the staff for their kind and skillful support.

Finally, the author thanks Drs. Yoshiaki Mayanagi and Kazuyoshi Yajima for giving me a chance for these experiments, and Saeko Ueno for her patience and understanding.

REFERENCES

Aaslid, R., Markwalder, T. M., and Nornes, H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J. Neurosurgery, 57: 769-774, 1982.

Aratow, M., Frotney, S. M., Watenpaugh, D. E., Crenshaw, A. G., and Hargens, A. R. Transcapillary fluid resonses to lower body negative pressure. J. Appl. Physiol., 74(6): 2763-2770, 1993.

Arridge, S. R., Cope, M., and Delpy, D. T. The theoretical basis for the determination of optical pathlengths in tissue: temporal and frequency analysis. Phys. Med. Biol., 37: 1531-1560, 1992.

Bartok, J. J., Loren, M. S., Carlson, D. D., and Walters, R. F. Cardiovascular Changes During Tilt and Leg Negative Pressure Tests. Aerospace Med., 39: 1157-1162, 1968.

Brinkley, J. W. and Raddin, J. H. Biodynamics: Transitory Acceleration. In: Fundamentals of Aerospace Medicine, edited by DeHart, R. L. Philadelphia:Lea & Febiger, 162-201, 1985.

Brooks, D. J., Redmond, S., Mathias, C. J., Bannister, R., and Symon, L. The effect of orthostatic hypotension on cerebral blood flow and middle cerebral artery velocity in autonomic failure with observations on the action of ephedrine. J. Neurol. Neurosurg Psychiatry, 52: 962-966, 1989.

Bryan, A. C., Macnamara, W. D., Simpson, J., and Wagner, H. N. Effects of acceleration on the distribution of pulmonary blood flow. J. Appl. Physiol., 20: 1129-1132, 1965.

Burton, R. R., Leverett, S. D., and Michaelson, E. D. Man at high sustained +Gz. Aerospace Medicine, 45: 1115-1136, 1974.

Burton, R. R. and Winnery, J. E. Operational G-induced loss of consciousness: something new, something old. Aviat. Space Environ. Med., 56: 812-817, 1985.

Burton, R. R. and Smith, A. H. Adaptation to acceleration environments. In: Handbook of Physiology: Environmental Physiology, edited by Fregly, M. J. and Blatteis, C. M. New York:Oxford University Press, Chapter 40: 943-970, 1996.

Cui, W., Kumar, C., and Chance, B. Experimental study of migration depth for the photons measured at sample surface. SPIE, 1431: 180-191, 1991.

Delpy, D. T., Cope, M., vanderZee, P., Arridge, S., Wray, S., and Wyatt, J. Estimation of optical pathlength through tissue from direct time of flight measurement. Phys. Med. Biol., 33: 1433-1442, 1988.

Fog, M. Cerebral circulation. Arch. Neurol. Psychiatry, 37: 351-64, 1937.

Furuhata, H., Kanno, R., and Kadaira, K. An ultrasound Doppler blood flow meter to measure the absolute volume flow rate. Proc.s third European congress on ultrasonics in medicine, Bologna, 227-229, 1978.

Gibbs, E. L., Lennox, W. G., and Nims, L. F. Arterial and cerebral venous blood. J. Biol. Chem., 144: 325-332, 1942.

Gibbs, J. M., Wise, R. J. S., Leenders, K. L., and Jones, T. Evaluation of cerebral perfusion reserve in patients with carotid artery occlusion. Lancet, i: 182-186, 1984.

Gilbert, C. A. and Stevens, P. M. Forearm vascular responses to lower body negative pressure and orthostasis. J. Appl. Physiol., 21: 1265-1272, 1966.

Glaister, D. H. Current and emerging technology in G-LOC detection: noninvasive monitoring of cerebral microcirculation using near infrared. Aviat. Space Environ. Med., 59: 23-28, 1988.

Gratton, G., Maier, J. S., Fabiani, M., Mantulin, W. W., and Gratton, E. Feasibility of intracranial near-infrared optical scanning. Psychophysiol., 31: 211-215, 1994.

Guyton, A. C. Vascular distensibility and functions of the arterial and venous systems. In: Textbook of medical physiology., edited by Guyton, A. C. :Phyladelphia, 159-169, 1991.

Heistad, D. D. and Kontos, H. A. Cerebral circulation (chap 5). In: Handbook of Physiology (Sec.2, Vol.3), edited by Shepherd, J. T., Abboud, F. M., and Geiger, S. R. :NewYork, 137-182, 1983.

Hiraoka, M., Firbank, M., Essenpreis, M., Cope, M., Arridge, S. R., vanderZee, P., and Delpy, D. T. A Monte Carlo investigation of optical pathlength in inhomogeneous tissue and its application to near-infrared spectroscopy. Phys. Med. Biol., 38: 1859-1876, 1993.

Howard, P. The physiology of positive acceleration. In: A textbook of aviation physiology, edited by Gilles, J. A. New York: Pergamon Press, 551-687, 1965.

Jobsis, F. F. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science Washington DC, 198: 1264-1267, 1977a.

Jobsis, F. F., Keizer, J. H., Lamanna, J. C., and Rosenthal, M. Reflectance spectrophotometry of cytochrome aa^3 in vivo. J. Appl. Physiol., 43: 858-872, 1977b.

Jobsis, F. F. Non-invasive near infrared monitoring of cellular oxygen sufficiency in vivo. Adv. Exp. Med. Biol., 191: 833-842, 1986.

Jorgensen, L. G., Perko, M., Perko, G., and Secher, N. H. Middle cerebral artery velocity during head-up tilt induced hypovolaemic shock in humans. Clin. Physiol., 13(4): 323-336, 1993.

Kapoor, W. N., Smith, M. A., and Miller, N. L. Upright tilt testing in evaluating syncope: a comprehensive literature review. The American Journal of Medicine, 97: 78-88, 1994.

Kristiansen, K. and Krog, J. Electromagnetic studies on the blood flow through the carotid system in man. Neurol., 12: 20-23, 1962.

Larsen, F. S., Olsen, K. S., Hansen, B. A., Paulson, O. B., and Knudsen, G. M. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. Stroke., 25(10): 1985-1988, 1994.

Leftheriotis, G., Mougeolle, J. L., Victor, J., Dupuis, J. M., Tadei, A., and Saumet, J. L. Circulatory changes of the middle cerebral artery during syncopes produced by the head-up tilt test. Presse Medicale, 21: 1663-1667, 1992.

Leverett, S. D. and Whinnery, J. E. Biodynamics: Sustained Acceleration. In: Fundamenetals of Aerospace Medicine, edited by DeHart, R. L. Philadelphia:Lea & Febiger, 202-249, 1985.

Lightfoot, J. T., Hilton, F. J. r., and Fortney, S. M. Repeatability and protocol comparability of presyncopal symptom limited lower body negative pressure exposures. Aviat. Space Environ. Med., 62: 19-25, 1991.

Mukai, C. N., Lathers, C. M., Charles, J. B., and Bennett, B. S. Cardiovascular responses to repetitive exposure to hyper- and hypogravity states produced by parabolic flight. J. Clin. Pharmacol., 34(5): 472-479, 1994.

Murray, R. H., Krog, J., Carlson, L. D., and Bowers, J. A. Cumulative effects of venesection and lower body negative pressure. Aerospace Med., 38: 243-247, 1967.

Musgrave, F. S., Zechman, F. W., and Mains, R. C. Changes in total leg volume during lower body negative pressure. Aerospace Med., 40: 602-606, 1969.

Musgrave, F. S., Zechman, F. W., and Mains, R. C. Comparison of the effects of 70 Tilt and several levels of lower body negative pressure on heart rate and blood pressure in man. Aerospace Med., 42(10): 1065-1069, 1971.

Nicogossian, A. E. and Robbins, D. E. Characteristics of The Space Environment. In: Space Physiology and Medicine, edited by Nicogossian, A. E., Huntoon, C. L., and Pool, S. L. Philadelphia:Lea & Febiger, 50-62, 1994.

Olesen, J. Quantitative Evaluation of Normal and Pathologic Cerebral Blood Flow Regulation to Perfusion Pressure. Arch. Neurol., 28: 143-150, 1973.

Ossard, G., Clere, J. M., Kerguelen, M., Melchior, F., and Seylaz, J. Response of human cerebral blood flow to +Gz accelerations. J. Appl. Physiol., 76(5): 2114-2118, 1994.

Powers, W. J., Grubb, R. L. J. r., and Raichle, M. E. Physiological responses to focal cerebral ischemia in humans. Ann. Neurol., 16: 546-552, 1984.

Raven, P. B., Young, D. R., and Blomqvist, C. G. Physical fitness and cardiovascular response to lower body negative pressure. J. Appl. Physiol., 56(1): 138-144, 1984.

Samueloff, S. L., Browse, N., and Shepherd, J. T. Responses of capacity vessels in human limbs to head-up tilt and suction on lower body. J. Appl. Physiol., 21: 47-54, 1966.

Scheinberg, P. and Stead, E. The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow oxygen utilization, glucose utilization, and peripheral resistance, with observations on the effect of tilting and anxiety. J. Clin. Invest., 28: 1163-1171, 1949.

Shenkin, H. A., Scheuermann, W. G., Spitz, E. B., and Groff, R. A. Effect of Change of Position upon the Cerebral Circulation of Man. J. Appl. Physiol., 2: 317-326, 1950.

Shvartz, E. and Meyerstein, D. Tilt Tolerance of Young Men and Young Women. Aerospace Med., 40: 253-255, 1970.

Stevens, P. M. and Lamb, L. E. Effects of lower body negative pressure on the cardiovascular system. Am. J. Cardiol., 16: 506-515, 1965.

Tripathi, A. and Nadel, E. R. Forearm skin and muscle vasoconstriction during lower body negative pressure. J. Appl. Physiol., 60(5): 1535-1541, 1986.

Uematsu, S. Determination of volume of arterial blood flow by an ultrasonic device. J. Clin. Ultrasound., 9: 209-216, 1981.

Wang, J., Marshall, R. J., and Shepherd, J. T. The effect of changes in posture and of great exercise on stroke volume in man. J. Clin. Invest., 39: 1051, 1960.

Watenpaugh, D. E. and Hargens, A. R. The Cardiovascular System in Microgravity. In: Handbook of Physiology: Environmental Physiology, edited by Fregly, M. J. and Blatteis, C. M. New York:Oxford University Press, Chapter 29: 631-674, 1996.

Werchan, P. M. Physiologic basis of G-induced loss of consciousness (G-LOC). Aviat. Space Environ. Med., 62: 612-614, 1991.

Wolthuis, R. A., Hoffler, G. W., and Johnson, R. L. Lower body negative pressure as an assay technique for orthostatic tolerance:1. the individual response to a constant level (-40 mmHg) of LBNP. Aerospace Med., 41(1): 29-35, 1970.

Wolthuis, R. A., LeBlanc, A., Carpentier, W. A., and Bergman, S. A. J. r. Response of local vascular volumes to lower body negative pressure stress. Aviat. Space Environ. Med., 46(5): 697-702, 1975.

Wyatt, J. S., Cope, M., Delpy, D. T., Wray, S., and Reynolds, E. O. R. Quantification of cerebral oxygenation and hemodynamics in sick newborn infants by near infrared spectrophotometry. Lancet, ii: 1063-1066, 1986.

APPENDIX A: Mathematical Principle of measuring the flow velocity independently of the transducer angle

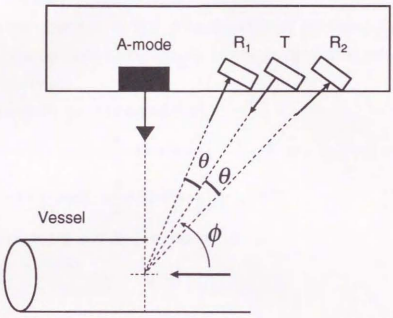


Figure. A1 A diagram of the carotid Doppler flowmeter (modified from Uematsu, 1981).

The brief outline of the mathematical principle is already shown in the paper written by Uematsu. For readers' convenience, the author here presents some modified equations based upon the Uematsu's explanations in order to explain the principal in an easier way.

Based upon the principle of the Doppler shift, we can express the shifts of the receiving ultrasound as

$$Fd_1 = h\ V \mathrm{Cos}\left(\phi + \frac{\theta}{2}\right) \quad \text{..... (1)}$$

$$Fd_2 = h\ V \mathrm{Cos}\left(\phi - \frac{\theta}{2}\right) \quad \text{..... (2)}$$

where Fd_1 and Fd_2 are the Doppler shifts at the transducer R_1 and R_2, respectively, and where V is the blood flow velocity. Also, the value of h is defined as $2\ Ft\ /\ C$ where Ft and C are the transmitting ultrasound frequency and the velocity of ultrasound, respectively.

Equation (1) and (2) can be expanded as

$$Fd_1 = h\ V\left(\mathrm{Cos}\phi \mathrm{Cos}\frac{\theta}{2} - \mathrm{Sin}\phi \mathrm{Sin}\frac{\theta}{2}\right) \quad \text{..... (1)'}$$

$$Fd_2 = h\ V\left(\mathrm{Cos}\phi \mathrm{Cos}\frac{\theta}{2} + \mathrm{Sin}\phi \mathrm{Sin}\frac{\theta}{2}\right) \quad \text{..... (2)'}$$

From the equation (1)' and (2)', we obtain

$$\mathrm{Sin}\phi = \frac{a+b}{2\ h\ V\ \mathrm{Cos}\theta/2}, \quad \mathrm{Cos}\phi = \frac{a-b}{2\ h\ V\ \mathrm{Sin}\theta/2}$$

$$\therefore \quad \left(\frac{a+b}{2\ h\ V\ \mathrm{Cos}\theta/2}\right)^2 + \left(\frac{a-b}{2\ h\ V\ \mathrm{Sin}\theta/2}\right)^2 = 1$$

Solving the above equation for V, we obtain

$$V = \frac{1}{2h}\sqrt{\left(\frac{a+b}{\mathrm{Cos}\theta/2}\right)^2 + \left(\frac{a-b}{\mathrm{Sin}\theta/2}\right)^2}$$

Using $\mathrm{Cos}2\theta = 1 - 2\mathrm{Sin}^2\theta = 2\mathrm{Cos}^2\theta - 1$, we finally obtain

$$V = \frac{\sqrt{a^2 + b^2 - 2ab\mathrm{Cos}\theta}}{h\ \mathrm{Sin}\theta}$$

Accordingly, by the carotid Doppler flowmeter, we can obtain the flow velocity independently of the angle between the transducer and the vessel.

APPENDIX B: Principle of Near Infrared Spectrophotometer

Assuming that light goes straight through a medium consisting of a homogenous component, the attenuation of the light can be express as

$$\frac{d}{dx}I(x) = -\alpha(\lambda)\,\varepsilon\,I(x) \qquad \therefore\ \log\frac{Ii(\lambda)}{Io(\lambda)} = \alpha(\lambda)\,\varepsilon\,l$$

where $I(x)$ is the intensity of light at the distance x, and where $Ii(\lambda)$ and $Io(\lambda)$ are the intensity of the transmitting and receving light, respectively, and also where $\alpha(\lambda)$, ε, and l are an absorption coefficient of the light at the wavelength λ, concentration of the component, and a pathlength, respectively.

If light goes through a medium that consists of 'n' separate components, the above equation is rewritten as

$$\log\frac{Ii(\lambda)}{Io(\lambda)} = l\sum_{k=1}^{n}\alpha_k(\lambda)\,\varepsilon_k \quad \cdots\cdots\cdots (1)$$

where $\alpha_k(\lambda)$ and ε_k are absorption coefficients of each component at the wavelength λ and concentrations of each component (k = 1, ... n-1, n), respectively. However, light cannot go straight because biological tissue highly scatters photon traveling in it. For this reason, to the right part of the equation (1), we have to add the term X that represents the loss of light. Also, due to the scattering effect, the light migrates considerably further through the tissue than the direct distance between the transmitting and receiving optodes. Thus, the equation (1) can finally be rewritten as

$$\log\frac{Ii(\lambda)}{Io(\lambda)} = l'\sum_{k=1}^{n}\alpha_k(\lambda)\,\varepsilon_k + X \quad \cdots\cdots\cdots (2)$$

where l' is the averaged optic pathlength. Concentration of the components and wavelength of the light are the factors which possibly affect the averaged optic pathlength and the scattering effects. However, their effects are negligible in usual physiological experiments.

Then we can rewrite the equation (2) as

$$\Delta \log \frac{Ii(\lambda)}{Io(\lambda)} = l' \sum_{k=1}^{n} \alpha_k(\lambda)\, \Delta\varepsilon_k \quad \cdots\cdots\cdots (3)$$

where Δ represents changes from the starting values. If we measure the changes in photoabsorption at more than 'n' separate wavelengths, the concentration of each component can be calculated from the equation (3) by a least square method. Thus we finally obtain the changes from the starting values in the concentration of each components.

APPENDIX C: Circulation model to analyze the data of NIRS

The author describes here a new method to provide continuous data for CBF with NIRS, in which two optodes were placed on the forehead. The NIRS principle, as described elsewhere (Jobsis, 1977; Wyatt, 1986), depends upon the absorption by hemoglobin of near infrared light transmitted through the tissues of interest. The quantity of hemoglobins calculated from the absorption changes by NIRS ([*oxy*], [*deoxy*]) represent the changes from the initial values. Absolute values for hemoglobins per unit of brain tissue ([HbO_2], [*Hb*]) can be expressed as the formula given below:

$$[HbO_2] = [HbO_2]_{t=0} + k\,[oxy]$$

$$[Hb] = [Hb]_{t=0} + k\,[deoxy] \qquad ;\ k = \text{constant} \quad \text{--- (1)}$$

where $[HbO_2]_{t=0}$ and $[Hb]_{t=0}$ are the absolute values for the quantity of hemoglobins per unit of brain tissue at the start of measurement.

In the present model, cerebral circulation is divided into two compartments: the arterial and venous. Although anatomically inaccurate, this assumption seems valid in regard to the hemoglobin changes in the whole brain. Considering the in-out balance of the hemoglobin quantity in each compartment, the changes in both oxygenated and the deoxygenated hemoglobin quantities are given by

$$\frac{d}{dt}[HbO_2] = Qa - SvO_2 \cdot Qv - M \qquad ---(2)$$

$$\frac{d}{dt}[Hb] = (1 - SvO_2) \cdot Qv - M \qquad ---\ (3)$$

where SvO_2 is oxygen saturation at the venous blood, which can be expressed as $SvO_2 = [HbO_2]v / ([HbO_2]v + [Hb]v) = ([HbO_2] - [HbO_2]a) / ([HbO_2] + [Hb] - [HbO_2]a)$ --- (4) (Qa: blood flow into the arterial compartment (CBF), Qv: blood flow out of venous compartment (venous drainage), $[HbO_2]a$: oxygenated hemoglobin in the

arterial compartment, $[HbO_2]v$: oxygenated hemoglobin in the venous compartment, $[Hb]v$: deoxygenated hemoglobin in the venous compartment).

Using equations (2), (3), and (4),

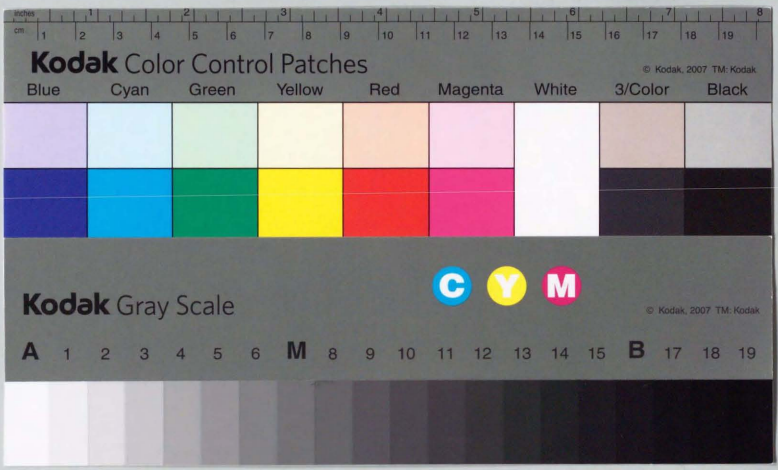
$$Qa = \frac{d}{dt}[HbO_2] - \frac{[HbO_2] - [HbO_2]a}{[Hb]} \cdot \frac{d}{dt}[Hb] + \frac{[HbO_2] + [Hb] - [HbO_2]a}{[Hb]} M$$

$$Qv = \frac{[HbO_2] - [HbO_2]a}{[HbO_2] + [Hb] - [HbO_2]a} \cdot (-\frac{d}{dt}[Hb] + M)$$

The initial parameters are assigned to the following: total hemoglobin quantity ($[HbO_2]a_{t=0} + [HbO_2]v_{t=0} + [Hb]v_{t=0}$) = 0.52 gram hemoglobin/100 g brain (Kuhl, 1975); the ratio of the arterial and the venous blood (Guyton, 1991) is 1 : 3, that is $[HbO_2]a_{t=0}$: ($[HbO_2]v_{t=0} + [Hb]v_{t=0}$) = 1 : 3; oxygen saturation of the venous blood is approximately 65% (Gibbs et al., 1942), that is $[HbO_2]v_{t=0}$: $[Hb]v_{t=0}$ = 2 : 1. Cerebral metabolic ratio of oxygen is 0.043 g hemoglobin/100 g brain/sec (Sheinberg et al., 1949; 1.36 ml O_2 can combine with 1 gram hemoglobin), which is assumed to remain constant. Blood volume in the arterial compartment can be expressed as $[HbO_2]a = [HbO_2]a_{t=0} + \Delta[HbO_2]a$.

The data calculated by this method are expressed as absolute values. However, it seems difficult to compare individual data between subjects because the initial parameters are assigned based upon the previously reported data. In spite of this limitation, the advantage of this method is to provide continuous data on CBF changes. This method seems helpful in analyzing the data given by NIRS.

LIST OF FIGURES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White
3/Color
Black
Kodak Gray Scale
C
Y
M
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A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19