Time-Dependent Changes in Cerebral Blood Flow and Arterial Pressure During Mild +G_z Hypergravity

Toru Konishi; Takuya Kurazumi; Tomokazu Kato; Chiharu Takko; Yojiro Ogawa; Ken-ichi Iwasaki

BACKGROUND: Artificial hypergravity has been proposed to prevent or treat various forms of physiological deconditioning experienced during spaceflight. We have previously reported that cerebral blood flow decreased at 15−21 min of +1.5-G_z centrifugation without decreases in arterial pressure at heart level. We reanalyzed our previous data to clarify time-dependent changes in cerebral blood flow and arterial pressure during mild +G_z hypergravity.

METHOD: We reanalyzed data for 0–20 min during +1.5-G_z centrifugation on 13 male subjects for whom physiological data were steadily recorded. Mean cerebral blood flow velocity in the middle cerebral artery ($MCBFV_{MCA}$), mean arterial pressure at heart level (MAP_{heart}), and middle cerebral artery level (MAP_{MCA}) during centrifugation were averaged every 5 min and compared with prehypergravity data (+1.0 G_z, 5 min).

RESULTS: MAP_{heart} did not change significantly, but MAP_{MCA} decreased significantly throughout centrifugation compared to prehypergravity data (−16.7% to −24.7%). $MCBFV_{MCA}$ tended to be decreased at 0–5 min of +1.5-G_z centrifugation (−3.3%), but this was not statistically significant. $MCBFV_{MCA}$ was significantly decreased at 5–10 min (−5.5%). $MCBFV_{MCA}$ at 10–15 min and 15–20 min were also significantly decreased to almost the same level (−6.9% and −6.8%, respectively).

DISCUSSION: No significant change in MAP_{heart} was detected, whereas MAP_{MCA} decreased significantly from the beginning of +1.5-G_z centrifugation. On the other hand, $MCBFV_{MCA}$ gradually decreased and became roughly flat in the latter half of 20-min centrifugation. Understanding the different time-dependent changes in cerebral blood flow and arterial pressure under mild +G_z hypergravity might be important for implementation of centrifuging as a countermeasure for spaceflight-induced deconditioning.

KEYWORDS: short-arm human centrifuge, artificial hypergravity, cerebrovascular hemodynamics, cerebral autoregulation.

Konishi T, Kurazumi T, Kato T, Takko C, Ogawa Y, Iwasaki K. *Time-dependent changes in cerebral blood flow and arterial pressure during mild +Gz hypergravity*. Aerosp Med Hum Perform. 2018; 89(9):787–791.

For more than 30 yr, intermittent exposure to artificial hypergravity generated by a short-arm human centrifuge during spaceflight or after returning to Earth has been proposed for preventing or treating spaceflight-induced deconditioning.[2] However, no consensus has been reached on the appropriate centrifugation protocol in countermeasures for spaceflight-induced deconditioning.[3] To establish an appropriate centrifugation protocol for astronauts, more research regarding not only the utility, but also the adverse effects of artificial hypergravity during centrifugation would be needed.[6,15]

Our research group previously evaluated changes in cerebrovascular circulation under a mild +G_z hypergravity environment generated by a short-arm human centrifuge. We reported that cerebral blood flow velocity in the middle cerebral artery (MCA) as monitored by transcranial Doppler ultrasonography (TCD) was significantly decreased at 15–21 min of +1.5-Gz centrifugation compared with prehypergravity (+1.0 G_z) data, whereas mean arterial pressure at heart level (MAP_{heart}) was not significantly changed.[6] However, that previous report evaluated cerebrovascular circulation only in the last 6 min of the 21-min centrifugation. Also, no reports have evaluated the time course

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This manuscript was received for review in February 2018. It was accepted for publication in June 2018.

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DOI: https://doi.org/10.3357/AMHP.5106.2018

of changes in cerebrovascular circulation under a mild $+G_z$ hypergravity environment. How cerebral blood flow changes with time under mild $+G_z$ hypergravity thus remains unclear. Several possibilities exist regarding this time-dependent change. For example, cerebral blood flow may gradually decrease from the beginning of centrifugation, or may show a rapid initial decrease followed by gradual restoration. To reveal time-dependent changes in cerebral blood flow and arterial pressure under a mild $+G_z$ hypergravity environment, we reanalyzed data for 0–20 min during centrifugation from our previous research.

METHODS

Subjects

This research was approved by the institutional review board of Nihon University School of Medicine (Itabashi-ku, Tokyo, Japan; No. 27-6-1; 20 June 2017). All procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent and medical history were provided by all study participants.

We reanalyzed data for 0–20 min in 13 male subjects with a mean ($\pm$ SD) age of 23 $\pm$ 2 yr (range, 20–27 yr), mean height of 171 $\pm$ 6 cm (range, 159–180 cm), and mean weight of 63.6 $\pm$ 6.7 kg (range, 48.6–77.7 kg) for whom physiological data were steadily recorded throughout centrifugation among a total of 15 subjects exposed to $+1.5\ G_z$ for 21 min using a short-arm human centrifuge in our original study.[6]

Equipment

The details are described in our previous report.[6] Briefly, continuous arterial pressure in the left radial artery at heart level was monitored by tonometry on a beat-to-beat basis (JENTOW 7700; Colin, Aichi, Japan). Cerebral blood flow velocity in the MCA was measured by TCD (WAKI; Atys Medical, St. Genislaval, France). Partial pressure of expiratory carbon dioxide was monitored by an infrared CO_2 sensor (OLG-2800; Nihon Kohden, Tokyo, Japan). Commercial software (Notocord-hem 3.3; Notocord, Paris, France) was used for recording each waveform of continuous arterial pressure and cerebral blood flow velocity with a 1-kHz sampling rate.

Procedure

The human centrifuge (radius, 1.7 m; Daiichi Medical, Tokyo, Japan) at Nihon University was used in this study. A gimbaled cabin was fixed at the end of the rotating arm and the subject was seated facing the outside in the cabin. The cabin pitched back at the heart level of the subject during centrifugation. Therefore, the resultant vector of the gravitational force of Earth and the centrifugal force was aligned with the longitudinal axis (head-to-foot) of the subject. Before centrifugation, prehypergravity ($+1.0\ G_z$) data were collected after 15 min of quiet rest in an upright sitting position in the cabin. Subjects were then exposed to an artificial hypergravity environment generated by the centrifuge for 21 min. Centrifugation was kept at 24.3 rpm to generate the $+1.5\ G_z$ at the heart level of the subject with an onset rate of $+0.5\ G \cdot min^{-1}$.

Although various physiological data were collected in the previous original research, we focused on time-dependent changes in mean cerebral blood flow velocity at MCA level ($MCBFV_{MCA}$), MAP_{heart}, mean arterial pressure at MCA level (MAP_{MCA}), and end-tidal carbon dioxide ($P_{ET}CO_2$) in this reanalysis. Because the expiratory CO_2 waveform of 1 subject was partially unrecorded, data from 12 subjects were used for the analysis of $P_{ET}CO_2$. Beat-to-beat values of $MCBFV_{MCA}$ and MAP_{heart} were obtained from each waveform of continuous arterial pressure and cerebral blood flow velocity. To calculate the hydrostatic pressure between heart level and MCA level, the distance between heart and eye was measured. Hydrostatic pressure was estimated as the measured distance multiplied by 0.76 mmHg at $+1.0\ G_z$ or 1.14 mmHg at $+1.5\ G_z$. MAP_{MCA} was then estimated by subtracting hydrostatic pressure from MAP_{heart}.

Data during the 21 min of centrifugation was divided into four sections of 5-min intervals from the point at which the magnitude of hypergravity reached $+1.5\ G_z$: 0–5 min, 5–10 min, 10–15 min, and 15–20 min. A total of five sections, including the prehypergravity section ($+1.0\ G_z$) and these four sections ($+1.5\ G_z$) was used to evaluate time-dependent changes. Averaging data during each data section obtained 5-min averages for $MCBFV_{MCA}$, MAP_{heart}, MAP_{MCA}, and $P_{ET}CO_2$.

Statistical Analysis

Normality was confirmed using the Shapiro-Wilk normality test. One-way repeated-measures analysis of variance was performed with a factor of section (prehypergravity, 0–5 min, 5–10 min, 10–15 min, and 15–20 min), followed by Holm's post hoc test. Statistical significance was set at the level of $P < 0.05$. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[7] Data are shown as mean $\pm$ SD.

RESULTS

Table I shows 5-min averages of $MCBFV_{MCA}$, MAP_{heart}, MAP_{MCA}, and $P_{ET}CO_2$ in each section. MAP_{heart} did not change significantly [$F(4,48) = 1.331$, $P = 0.271$ (ANOVA)]. However, MAP_{MCA} significantly decreased throughout centrifugation (range −16.7% to −24.7%) [$F(4,48) = 17.602$, $P < 0.001$ (ANOVA)], with no significant differences seen during centrifugation. **Fig. 1** shows time-dependent changes in $MCBFV_{MCA}$. $MCBFV_{MCA}$ showed a significant main effect of section [$F(4,48) = 15.030$, $P < 0.001$ (ANOVA)]. $MCBFV_{MCA}$ tended to decrease from the beginning of the +1.5-G_z centrifugation, but $MCBFV_{MCA}$ at the 0–5 min section did not reach statistical significance compared to the prehypergravity section [−3.3%, $P = 0.131$ (Holm's test)]. $MCBFV_{MCA}$ at 5–10 min was significantly decreased compared to the prehypergravity section [−5.5%, $P = 0.002$ (Holm's test)]. $MCBFV_{MCA}$ at 10–15 min and 15–20 min were also significantly decreased compared to the prehypergravity section [−6.9%, $P < 0.001$ (Holm's test)

Table I. 5-min Averages of Cerebral Blood Flow Velocity, Mean Arterial Pressure, and Partial Pressure of End-Tidal Carbon Dioxide Before and During +1.5-G_z Centrifugation.

	+1.0 G_Z	+1.5 G_Z				
	PREHYPERGRAVITY AVERAGE	0–5 MIN AVERAGE	5–10 MIN AVERAGE	10–15 MIN AVERAGE	15–20 MIN AVERAGE	ANOVA
MAP_{heart} (mmHg)	75.4 ± 8.0	75.1 ± 8.9	74.1 ± 8.3	76.1 ± 8.3	77.9 ± 9.6	0.271
MAP_{MCA} (mmHg)	52.0 ± 7.8	40.1 ± 9.3 ***	39.0 ± 8.6 ***	41.0 ± 8.4 **	42.9 ± 9.4 *	< 0.001
$MCBFV_{MCA}$ ($cm \cdot s^{-1}$)	63.5 ± 12.8	61.0 ± 10.9	59.7 ± 11.0 **	58.8 ± 10.7 ***	58.8 ± 10.4 **	< 0.001
$P_{ET}CO_2$ (torr)	39.6 ± 3.1	35.4 ± 2.1 ***	35.4 ± 2.2 ***	35.0 ± 2.6 ***	34.9 ± 3.1 ***	< 0.001

Values are mean ± SD.
Prehypergravity average: average of prehypergravity 5-min section (+1.0 G_z); 0–5 min average, 5–10 min average, 10–15 min average, and 15–20 min average: 5-min average of the 0–5 min, 5–10 min, 10–15 min, and 15–20 min sections during +1.5-G_z centrifugation.
MAP_{heart}: mean arterial pressure at heart level; MAP_{MCA}: mean arterial pressure at the middle cerebral artery level; $MCBFV_{MCA}$: mean cerebral blood flow velocity at the middle cerebral artery level; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; ANOVA: *P*-value of one-way repeated-measures analysis of variance with the factor of the data section.
* $P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (*P*-value of Holm's post hoc test compared with prehypergravity average).
Because the respiratory CO_2 waveform from 1 subject was partially unrecorded, data from 12 subjects were used for the analysis of $P_{ET}CO_2$.

and −6.8%, $P = 0.003$ (Holm's test), respectively]. $MCBFV_{MCA}$ did not differ significantly between sections during centrifugation (0–5 min, 5–10 min, 10–15 min, and 15–20 min) (Fig. 1). $P_{ET}CO_2$ was significantly decreased throughout centrifugation (range −10.1% to −11.7%) [$F(4,44) = 32.547$, $P < 0.001$ (ANOVA)].

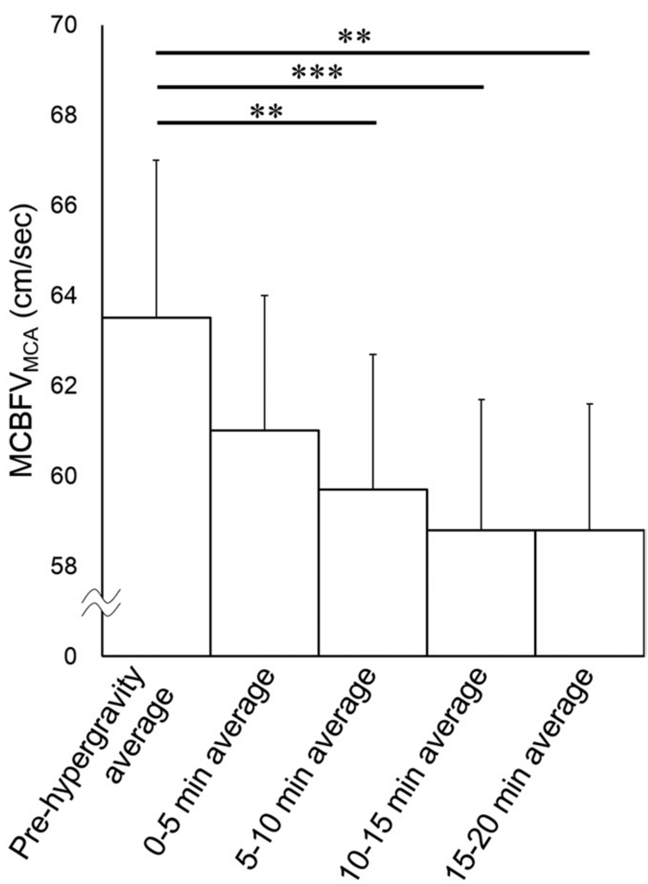

Fig. 1. Time-dependent change in mean cerebral blood flow velocity at the middle cerebral artery level ($MCBFV_{MCA}$). Prehypergravity average: average of prehypergravity 5-min section (+1.0 G_z); 0–5 min average, 5–10 min average, 10–15 min average, and 15–20 min average: 5-min average of 0–5 min, 5–10 min, 10–15 min, and 15–20 min sections during +1.5-G_z centrifugation. Values represent mean ± SE; **$P < 0.01$, ***$P < 0.001$ (*P*-value of Holm's post hoc test).

DISCUSSION

The aim of the present reanalysis was to evaluate time-dependent changes in cerebral blood flow and arterial pressure under a +1.5-G_z hypergravity environment. As a result, MAP_{heart} showed no significant change, but MAP_{MCA} decreased significantly from the beginning to the end of centrifugation. On the other hand, $MCBFV_{MCA}$ gradually decreased from the beginning of the +1.5-G_z centrifugation and reached statistical significance at 5–10 min. $MCBFV_{MCA}$ at 10–15 min was almost the same as $MCBFV_{MCA}$ at 15–20 min. Thus, $MCBFV_{MCA}$ seemed to reach a stable state, with no significant difference apparent between the last two segments.

Long-term exposure to a microgravity environment during spaceflight is known to lead to various forms of deconditioning. The development of effective, efficient countermeasures to such physiological deconditioning have increased in importance with the increasing duration of manned spaceflight. Intermittent exposure to the artificial hypergravity generated by a short-arm human centrifuge during spaceflight or after returning to Earth has been proposed for that purpose.[2] However, no consensus has been reached on the appropriate centrifugation protocol.[3] Many researchers have reported the effectiveness of artificial hypergravity against physiological deconditioning such as muscle atrophy,[16] bone loss,[9] and orthostatic intolerance.[10] To consider the appropriate centrifugation protocol, adverse effects under mild +G_z hypergravity should also be revealed, especially on cerebrovascular hemodynamics. Several reports have evaluated changes in cerebral blood flow velocity under the +G_z hypergravity environment using TCD.[8,12] These reports showed drastic decreases in cerebral blood flow velocity during exposure to hypergravity (−26% at +4.0 G_z for 10 s,[12] −48% at an average of +5.7 G_z during gradual-onset centrifugation[8]). However, subjects in those reports were exposed to high levels of +G_z hypergravity that would lead to prodromal symptoms (e.g., sweating, nausea, tunnel vision) for gravity-induced loss of consciousness and the duration of exposure to +G_z hypergravity was no longer than a few tens of seconds. Our research group has, therefore, been investigating the changes to cerebrovascular hemodynamics under sustained mild +G_z hypergravity.[6,11]

We previously evaluated circulatory dynamics under a +1.5-G_z hypergravity environment using healthy male subjects.[6] In that previous study, various physiological data were collected and compared between prehypergravity (+1.0 G_z) at the 6-min section before centrifugation and at 15–21 min during centrifugation. The report showed that cerebral circulation significantly changed even under mild +G_z hypergravity which would not lead to gravity-induced loss of consciousness or any significant change in MAP_{heart}. Because the previous study compared only two sections, the present reanalysis evaluated time-dependent changes in cerebral blood flow velocity and arterial pressure during 20 min of centrifugation. Understanding these time courses under mild +G_z hypergravity would be important when considering the future implementation of the short-arm centrifuge as a countermeasure for spaceflight-induced physiological deconditioning.

The present results show that $MCBFV_{MCA}$ gradually decreased and reached statistical significance after 5–10 min of +1.5 G_z centrifugation. Moreover, $MCBFV_{MCA}$ reached a stable state in the latter half of a 20-min centrifugation. The primary factor for decreases in $MCBFV_{MCA}$ was thought to be roughly 20% decreases in MAP_{MCA} throughout the centrifugation caused by increased hydrostatic pressure differences between heart and brain. However, these time courses of decreases in $MCBFV_{MCA}$ and MAP_{MCA} differed from each other. Moreover, reduction in $MCBFV_{MCA}$ were not large (maximum decrease, −6.9% at 10–15 min), whereas the reduction in MAP_{MCA} was −20.4% at 10–15 min. Cerebral autoregulation might be related to these differences in time-dependent changes and rate of change between $MCBFV_{MCA}$ and MAP_{MCA}. Although short-term spaceflight has not been seen to impair cerebral autoregulation,[5] long-term spaceflight could impair cerebrovascular autoregulation along with reduced CO_2 reactivity.[18] Furthermore, impairment of cerebral blood flow regulation has been reported in astronauts with orthostatic intolerance after short-term spaceflight.[1] Caution is therefore warranted when intermittent exposure to mild +G_z hypergravity is practically applied during long-term spaceflight. As subjects in the present study were younger than current astronauts, these findings might not be simply applicable to astronauts. For example, hypertension is an age-related change that would lead to further decreases in cerebral blood flow during centrifugation, because hypertension has been reported to impair cerebral autoregulation.[14] Moreover, elevated ambient CO_2 level and $P_{ET}CO_2$ in modern spacecraft[4] may also affect the changes in $MCBFV_{MCA}$. Details of the differences in time course between cerebral blood flow and arterial pressure under mild +G_z hypergravity should be elucidated to establish appropriate centrifugation protocols for astronauts under various scenarios in the future.

Other factors were thought to contribute to decreases in $MCBFV_{MCA}$ during mild +G_z hypergravity, including decreased cardiac output and venous return caused by blood pooling in the lower extremities.[17] Moreover, decreased $P_{ET}CO_2$ caused by changes in respiration[11] and vestibular stimulation due to continued rotation[13] may also be factors. In fact, $P_{ET}CO_2$ was significantly decreased at the beginning of centrifugation and remained decreased to almost the same level throughout centrifugation in the present study. Because the time course of $P_{ET}CO_2$ was not similar to that of $MCBFV_{MCA}$, simple explanation of changes in $MCBFV_{MCA}$ according to changes in $P_{ET}CO_2$ was difficult. Identifying the detailed causes for decreased $MCBFV_{MCA}$ is difficult, because the present reanalysis focused on only time-dependent changes in cerebral blood flow and arterial pressure.

Ossard et al. reported that $MCBFV_{MCA}$ did not decrease significantly during +2.0 G_z centrifugation (10 s)[12] and we therefore assumed that $MCBFV_{MCA}$ would not change during gradual onset acceleration (+0.5 G · min^{-1}) of our research protocol. To confirm this, we evaluated changes in $MCBFV_{MCA}$ during 1-min acceleration and confirmed that group averaged $MCBFV_{MCA}$ tended to increase rather than decrease.

Because this report was a reanalysis of a previous experiment that originally focused on the last 6 min of centrifugation, subjects were allowed to move the lower extremities during the initial 15 min of centrifugation, but were not allowed to move the head and arms, which were equipped with sensors. The reliability of physiological data in the early part of centrifugation might thus have been reduced compared to the latter part. A new research protocol that focuses on evaluating time-dependent changes in steady-state hemodynamics under mild +G_z hypergravity environment would be needed for stronger evidence.

MAP_{MCA} was simply estimated by subtracting hydrostatic pressure from MAP_{heart}. The possibility thus remains that changes in MAP_{MCA} might not have been identified due to other factors during centrifugation.

In conclusion, to clarify the time-dependent changes in cerebral blood flow and arterial pressure during 21 min of +1.5-G_z centrifugation, our previous research data were reanalyzed. As a result of our reanalysis, we found that $MCBFV_{MCA}$, MAP_{heart}, and MAP_{MCA} showed different patterns in time-dependent changes. No change was detected in arterial pressure at heart level under mild +G_z hypergravity, whereas arterial pressure at the MCA level decreased from the beginning of exposure. On the other hand, cerebral blood flow gradually decreased from the beginning, then became almost plateau after a certain period of time.

ACKNOWLEDGMENTS

This reanalysis was supported by MEXT Kakenhi Grant Number JP15H05939 for analysis and editing of the manuscript.

No conflicts of interest are declared by the authors.

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