

# Short-Term Volume Loading Effects on Estimated Intracranial Pressure in Human Volunteers

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

- BACKGROUND:** Short-term fluid loading is used as part of post-spaceflight medical procedures and clinical treatment in hospitals. Hypervolemia with hemodilution induced by rapid fluid infusion reportedly impaired dynamic cerebral autoregulation. However, the effects on intracranial pressure (ICP) remain unknown. Therefore, we estimated ICP noninvasively (nICP) to examine whether rapid fluid infusion would raise ICP.
- METHODS:** Twelve healthy male volunteers underwent two discrete normal saline (NS) infusions (15 and 30 ml · kg<sup>-1</sup> stages, NS-15 and NS-30, respectively) at a rate of 100 ml · min<sup>-1</sup>. The cerebral blood flow (CBF) velocity (CBFv) waveform from the middle cerebral artery obtained by transcranial Doppler ultrasonography was recorded, as was the arterial blood pressure (ABP) waveform at the radial artery obtained by tonometry. We then used these waveforms to calculate nICP, cerebral artery compliance, and the pulsatility index (PI) in an intracranial hydraulic model.
- RESULTS:** nICP increased significantly in both infusion stages from preinfusion (preinfusion: 7.6 ± 3.4 mmHg; NS-15: 10.9 ± 3.3 mmHg; NS-30: 11.7 ± 4.2 mmHg). No significant changes were observed in cerebral artery compliance or PI. Although ABP did not change in any stage, CBFv increased significantly (preinfusion: 67 ± 10 cm · s<sup>-1</sup>; NS-15: 72 ± 12 cm · s<sup>-1</sup>; NS-30: 73 ± 12 cm · s<sup>-1</sup>).
- DISCUSSION:** Hypervolemia with hemodilution induced by rapid fluid infusion caused increases in nICP and CBFv. No changes were observed in cerebral artery compliance or PI related to cerebrovascular impedance. These findings suggest that rapid fluid infusion may raise ICP with increased CBF.
- KEYWORDS:** cerebral circulation, cerebrospinal fluid pressure, fluid challenge, hypervolemia, normal saline infusion, non-invasive measurement.

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Volume replenishment is one of the basic medical treatments to stabilize hemodynamics.<sup>1</sup> To prevent postlanding syndrome or hypotension, short-term fluid loading is performed routinely by astronauts.<sup>6,29</sup> In recent years, the United States' orbital segment crews returning from the International Space Station using a Soyuz spacecraft frequently received intravenous infusions of normal saline, Ringer's lactate, and/or glucose fluids for a short period after landing.<sup>10</sup> In clinical treatment, an intravenous infusion of predetermined fluid volume over a short period of time (rapid fluid infusion) is one of the most common interventions for patients with suspected or predicted hypovolemia.<sup>1</sup> It is also called a "fluid challenge" in intensive care or perioperative management. Administration of 30 ml · kg<sup>-1</sup> of crystalloids is recommended for clinical suspicion of hypovolemia as an initial rapid fluid infusion.<sup>22</sup> Generally, hypervolemia accompanied by hemodilution is administered in

healthy participants during such rapid fluid infusion.<sup>21</sup> Some studies have reported that hemodilution increases cerebral blood flow (CBF) to maintain arterial oxygen delivery against decreased hematocrit.<sup>2,27</sup> In our previous study, hypervolemia with hemodilution by normal saline (NS) infusions for a short period impaired dynamic cerebral autoregulation and increased CBF velocity (CBFv).<sup>21</sup> Although increased CBF due to hypervolemia with hemodilution may potentially affect intracranial

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pressure (ICP), this effect has not been investigated. In our field of research for spaceflight associated neuro-ocular syndrome (SANS), data on ICP during rapid fluid infusion would be helpful.<sup>10,15</sup>

Noninvasive ICP (nICP) estimation based on a system analysis reflecting intracranial physiology has been developed for clinical patients.<sup>24,25</sup> Cerebral artery compliance and the CBF pulsatility index (PI) have also been used as parameters reflecting the changes in cerebral circulation or ICP based on an intracranial hydraulic model.<sup>28</sup> These three indices can be derived from precisely obtained arterial blood pressure (ABP) and CBFv waveforms, and are considered to reflect integral changes in ICP.<sup>12</sup> Therefore, in the present study, using these three indices, we examined the changes in ICP brought on by hypervolemia with hemodilution induced by rapid fluid infusion.

## METHODS

### Subjects

We analyzed the data from 12 healthy male volunteers (mean age  $\pm$  SD,  $21 \pm 1$  yr; height,  $172 \pm 4$  cm; weight,  $63 \pm 6$  kg) in our previous study investigating the effect of the change in central blood volume on autonomic hemodynamic regulation and cerebral autoregulation.<sup>21,23</sup> The aim of the present study was to investigate the effect of hypervolemia with hemodilution induced by rapid NS infusion on ICP by reanalyzing using our previous study's database. The original study protocol was approved by the Ethics Committee of the Nihon University School of Medicine (No. 5, December 14<sup>th</sup>, 2004), and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the original study. In addition, the present study was approved by the Ethics Committee of the Nihon University School of Medicine (P21-02-0, May 19<sup>th</sup>, 2021). We disclosed the present study via opt-out; no participant requested to withdraw from the study. The present study was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry as UMIN000044606.

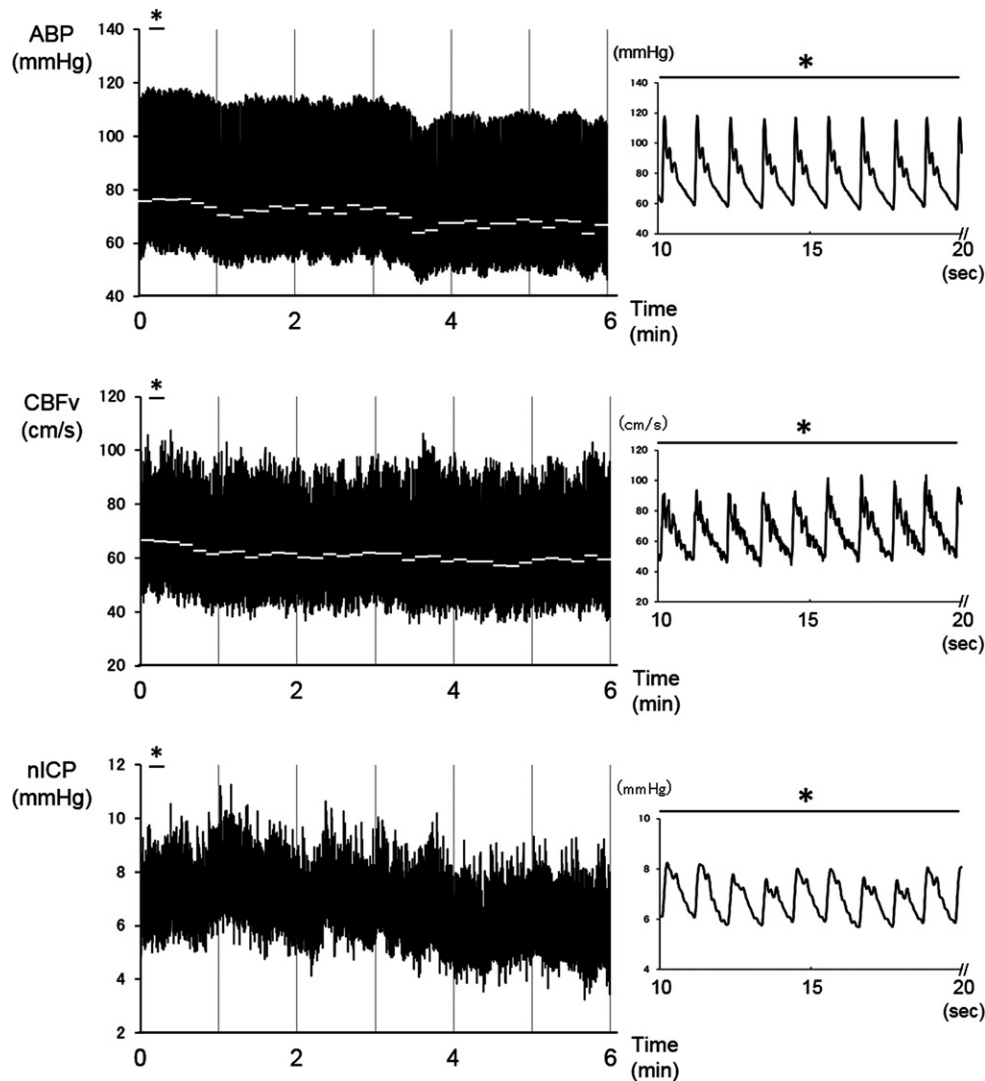
### Equipment and Procedures

Details of the procedures are described in a previous report.<sup>21,23</sup> All participants fasted for at least 2 h before the examination and refrained from heavy exercise and from consuming caffeinated or alcoholic beverages for at least 24 h before the examination. Heart rate (HR) with electrocardiography (ECG), arterial oxygen saturation by pulse oximetry ( $S_pO_2$ ), end-tidal carbon dioxide pressure ( $ETCO_2$ ), and respiratory rate (RR) were measured (Life Scope BSM-5132; Nihon Kohden, Tokyo, Japan). The continuous ABP waveform was obtained by tonometry (Jentow 7700; Colin, Aichi, Japan) from the radial artery, and the continuous CBFv waveform from the middle cerebral artery (MCA) was obtained by transcranial Doppler ultrasonography with a 2-MHz probe (WAKI; Atys Medical, St. Genislaval, France). Cardiac output (CO) was measured using an impedance cardiograph (CIC1000; Sobra Medical Systems,

Milwaukee, WI, USA). The measurement of central venous pressure (CVP) was performed via a central catheter (First PICC catheter, 18-gauge, 1.35 mm  $\times$  65 cm; Becton Dickinson, Franklin Lakes, NJ) inserted into an antecubital vein to the level of the superior vena cava and then connected to a pressure transducer (DX-312; Becton Dickinson) in six of the participants. The NS administration and blood collection were performed via an 18-gauge catheter inserted into a forearm vein. Before the two discrete NS infusion procedures, a lower-body negative-pressure (LBNP) procedure was performed. All participants rested for 15–20 min after the LBNP procedure and hemodynamic recovery was confirmed when HR and intermittent ABP values were similar to those before the LBNP procedure (a change in HR of fewer than 10 bpm and a change in intermittent ABP of less than 10 mmHg). Then the preinfusion measurement was recorded for 6 min in a supine position. Next, the first 15 ml  $\cdot$  kg<sup>-1</sup> of NS (NS-15) was administered at a rate of 100 ml  $\cdot$  min<sup>-1</sup>, followed by an additional 15 ml  $\cdot$  kg<sup>-1</sup> of NS (total 30 ml  $\cdot$  kg<sup>-1</sup>, NS-30) at the same rate. After the completion of each infusion, the 6-min measurements for NS-15 and NS-30 were recorded. The ABP and CBFv waveforms were recorded throughout each 6-min measurement at a sampling rate of 1 kHz and were resampled at 100 Hz using Noto-cord-Hem 3.3 software (Notocord, Paris, France). HR and CVP were averaged for each 6-min measurement.  $S_pO_2$ ,  $ETCO_2$ , and RR were recorded every minute during each 6-min measurement and were averaged for the 6-min period. CO was measured at the initiation of each 6-min measurement. Blood collection was performed immediately after the completion of each infusion to count hematocrit and hemoglobin concentration in five of the participants. The blood cell count was examined by a clinical laboratory (SRL CO, Tokyo, Japan).

### Data Analysis

Estimation of nICP was conducted using a mathematical model based on a system analysis reflecting intracranial physiology, in which the signal transformations from ABP to ICP are controlled by the relationship between ABP and CBF.<sup>24,25</sup> Resampled data of ABP and CBFv at 100 Hz were computed to “nICP Plugin” software (Klinkum Chemnitz GmbH, Chemnitz, Germany), as described previously.<sup>12</sup> First, based on the assumption that ABP was the input signal, the weight function between ABP and ICP (ABP–ICP) was computed. Second, the coefficients of the weight function between ABP and CBF (ABP–CBF) were calculated by a transfer function as hemodynamic characteristics. Finally, the relationship between ABP–ICP and ABP–CBF was calculated using multiple regression analysis; the output signal provided a full waveform of the estimated nICP (Fig. 1). The mathematical techniques in “nICP Plugin,” which consist of analytical methods in which the major component of the ICP wave was about 1 to 20 Hz frequency, demonstrated the greatest acceleration in transmission in ABP–ICP occurred at about 10 to 15 Hz, and there was high correlation between estimated ICP and actual ICP at this frequency.<sup>11</sup> A constant relationship between ABP–ICP and ABP–CBF transformations was derived from the analysis of a database with



**Fig. 1.** Measured arterial blood pressure and cerebral blood flow velocity waveforms and estimated waveform of noninvasive intracranial pressure from a representative subject. Left: time-series variations of measured ABP and CBFv, as well as estimated nICP during 6-min preinfusion measurement. Right: measured ABP and CBFv waveforms, and estimated nICP waveform during the asterisk 10-s window period (10 to 20 s as a representative). ABP: arterial blood pressure, CBFv: cerebral blood flow velocity, nICP: noninvasive intracranial pressure. Black line: waveforms of arterial blood pressure obtained by tonometry (top) and cerebral blood flow velocity obtained by transcranial Doppler (middle), and noninvasive intracranial pressure estimated using “nICP Plugin” software at 100 Hz. White bar: mean arterial blood pressure (top) and mean cerebral blood flow velocity (middle) for every 10-s window.

145 neurosurgical patients.<sup>24</sup> The reliability of the ABP-ICP transmission has been confirmed, as indicated by the highly coherent relationship between ABP and CBFv.<sup>13</sup> Although the nICP value may not be equal to the ICP value obtained invasively, the accuracy of the relative changes has been confirmed to be the same as that for the change in the invasive ICP value in neurosurgical patients.<sup>3</sup>

Cerebral artery compliance reflects changes in cerebral arterial blood volume in response to changes in ABP. The change in cerebral arterial blood volume over one cardiac cycle ( $\Delta CaBV(t)$ ) can be calculated in Eq. 1 as an integral of the difference between arterial inflow (= CBFv) and the moving average of CBFv. The relative change in cerebral artery compliance is then calculated based on the ratio between the pulsatile changes in ABP and  $\Delta CaBV$  in Eq. 2:<sup>28</sup>

$$\Delta CaBV(t) = \int_{t_0}^t (CBFv(s) - CBFv_{moving\ average}(s)) ds \quad \text{Eq. 1}$$

$$\text{Cerebral artery compliance} = \frac{\text{Amplitude}_{\Delta CaBV}}{\text{Amplitude}_{ABP}} \quad \text{Eq. 2}$$

PI is a descriptor of the CBFv amplitude over one cardiac cycle, calculated in Eq. 3.<sup>5</sup>

$$PI = \frac{CBFv_{systolic} - CBFv_{diastolic}}{CBFv_{mean}} \quad \text{Eq. 3}$$

The nICP estimation, the mathematical calculation of cerebral artery compliance and PI, and the average calculations of ABP and CBFv were performed in every 10-s window, and then the

values of 36 windows (total 6 min) were averaged (Fig. 1). Data analysis was performed using ICM+ version 8.1 (<http://www.neurosurg.cam.ac.uk/icmpls/>, Cambridge Enterprise, Cambridge, United Kingdom). The cerebral vascular resistance index (CVRI) was calculated according to Eq. 4 in six of the participants with measured CVP.<sup>5</sup>

$$\text{CVRI} = \frac{\text{mean ABP} - \text{mean nICP or CVP (whichever is greater)}}{\text{mean CBFv}} \quad \text{Eq. 4}$$

### Statistical Analysis

Data are presented as the mean  $\pm$  SD and were compared across the three stages (preinfusion, NS-15, and NS-30). The normal distribution of the data was assessed using the Kolmogorov–Smirnov test. For variables with a normal distribution, one-way repeated-measures analysis of variance (ANOVA) was performed. When the variables were not normally distributed, Friedman's repeated-measures ANOVA using ranks was performed. The Student-Newman-Keuls method was conducted as a post hoc test when significant differences occurred. Values of  $P < 0.05$  were considered statistically significant. All analyses were performed using SigmaStat version 3.11 (Systat Software Inc., San Jose, CA, USA).

### RESULTS

**Table I** shows three indices calculated by mathematical analyses reflecting the intracranial hydraulic model. The nICP values increased significantly from preinfusion ( $7.6 \pm 3.4$  mmHg) to both NS-15 ( $10.9 \pm 3.3$  mmHg,  $P = 0.005$ ) and NS-30 ( $11.7 \pm 4.2$  mmHg,  $P = 0.002$ ). No significant difference in nICP was found between NS-15 and NS-30 ( $P = 0.452$ ) [nICP,  $F(2, 11) = 8.394$ ,  $P = 0.002$ , ANOVA]. No significant changes in cerebral artery compliance or PI values were observed between the three stages [cerebral artery compliance,  $F(2, 11) = 2.391$ ,  $P = 0.115$ , ANOVA; PI,  $F(2, 11) = 1.678$ ,  $P = 0.210$ , ANOVA].

Hemodynamics, blood count, and respiratory conditions are shown in **Table II**. CBFv increased significantly from preinfusion to both NS-15 ( $P = 0.001$ ) and NS-30 ( $P = 0.002$ ). No significant difference in CBFv was found between NS-15 and NS-30 ( $P = 0.535$ ) [CBFv,  $F(2, 11) = 9.955$ ,  $P \leq 0.001$ , ANOVA]. CO also increased significantly from preinfusion to both NS-15 ( $P = 0.020$ ) and NS-30 ( $P < 0.001$ ), but no significant difference was observed between NS-15 and NS-30 ( $P = 0.091$ ) [CO,  $F(2, 11) = 10.349$ ,  $P \leq 0.001$ , ANOVA]. CVP

increased significantly at every infusion stage (NS-15, compared with preinfusion,  $P < 0.001$ ; NS-30, compared with preinfusion,  $P < 0.001$ , and compared with NS-15,  $P = 0.012$ ) [CVP,  $F(2, 5) = 40.206$ ,  $P \leq 0.001$ , ANOVA]. CVRI decreased significantly at NS-30 compared with preinfusion and NS-15 (compared with preinfusion,  $P = 0.033$ , and compared with NS-15,  $P = 0.041$ ) [CVRI,  $F(2, 5) = 4.986$ ,  $P = 0.031$ , ANOVA]. Hemoglobin and hematocrit decreased significantly at every infusion stage [hemoglobin, NS-15, compared with preinfusion,  $P < 0.05$ ; NS-30, compared with preinfusion,  $P < 0.05$ , and compared with NS-15,  $P < 0.05$ ;  $\chi^2 = 10.000$ ,  $P \leq 0.001$ , Friedman; hematocrit, NS-15, compared with preinfusion,  $P < 0.001$ ; NS-30, compared with preinfusion,  $P < 0.001$ , and compared with NS-15,  $P = 0.003$ ;  $F(2, 4) = 114.165$ ,  $P \leq 0.001$ , ANOVA]. No significant changes in ABP,  $S_pO_2$ , or  $ETCO_2$  were observed between the three stages [ABP,  $F(2, 11) = 2.500$ ,  $P = 0.105$ , ANOVA;  $S_pO_2$ ,  $\chi^2 = 3.231$ ,  $P = 0.199$ , Friedman;  $ETCO_2$ ,  $F(2, 11) = 1.265$ ,  $P = 0.304$ , ANOVA].

### DISCUSSION

The major finding of the present study is that hypervolemia with hemodilution induced by rapid fluid infusion increased nICP significantly in both infusion stages (NS-15 and NS-30) compared with preinfusion (**Fig. 2**). On the other hand, no changes were seen in cerebral artery compliance or PI throughout the two stages compared with preinfusion. Although ABP did not change during rapid fluid infusion in the present study, CBFv and CO increased in both infusion stages. Therefore, the rise in estimated ICP was considered to be caused by increased CBF, as indicated by the significant increases in CBFv during both NS infusions ( $15 \text{ mL} \cdot \text{kg}^{-1}$  and  $30 \text{ mL} \cdot \text{kg}^{-1}$ ).

Cerebral artery compliance is defined as the change in arterial blood volume in response to a change in pressure, and PI is a descriptor of CBFv pulse amplitude reflecting cerebrovascular impedance.<sup>28</sup> Thus, these indices have been used to assess changes in cerebral circulation or ICP.<sup>5,12</sup> The lack of changes in both of these indices in the present study suggests that the intracranial artery compliance and the intracranial pulsatile flow impedance do not change in hypervolemia with hemodilution induced by rapid fluid infusion. On the other hand, both infusions ( $15 \text{ mL} \cdot \text{kg}^{-1}$  and  $30 \text{ mL} \cdot \text{kg}^{-1}$ ) increased CBFv significantly. This could be the result of increased CO as well as decreased CVRI in hypervolemia due to fluid administration. Therefore,

**Table I.** Results of the Three Estimated Indices Reflecting Intracranial Pressure.

	PREINFUSION	NS-15	NS-30	P-VALUE
nICP (mmHg)	$7.6 \pm 3.4$	$10.9 \pm 3.3^*$	$11.7 \pm 4.2^*$	0.002 (A)
Cerebral artery compliance ( $\text{cm}^3 \cdot \text{mmHg}^{-1}$ )	$0.15 \pm 0.03$	$0.17 \pm 0.04$	$0.16 \pm 0.05$	0.115 (A)
PI (a.u.)	$0.81 \pm 0.09$	$0.78 \pm 0.08$	$0.81 \pm 0.10$	0.210 (A)

Data are presented as mean  $\pm$  SD. P-values are expressed as (A) ANOVA.

NS-15, administration of  $15 \text{ mL} \cdot \text{kg}^{-1}$  of normal saline; NS-30, administration of an additional  $15 \text{ mL} \cdot \text{kg}^{-1}$  (total  $30 \text{ mL} \cdot \text{kg}^{-1}$ ) of normal saline; nICP, noninvasive intracranial pressure estimated by plugin software "nICP Plugin"; PI, pulsatility index.

\*Shows post hoc test with the Student Newman-Keuls method;  $P < 0.01$  compared to preinfusion.



**Table II.** Hemodynamics Parameters, Blood Sampling, and Respiratory Measurements.

	PREINFUSION	NS-15	NS-30	P-VALUE
ABP (mmHg)	79 ± 9	86 ± 12	82 ± 10	0.105 (A)
CBFv (cm · s <sup>-1</sup> )	67.3 ± 10.5	72.1 ± 12.3 **	72.9 ± 12.2 **	<0.001 (A)
CVRI (mmHg · cm <sup>-1</sup> · s <sup>-1</sup> )	1.13 ± 0.25	1.10 ± 0.33	0.96 ± 0.24 *,†	0.031 (A)
HR (bpm)	58 ± 8	61 ± 10 ***	68 ± 10 ***	<0.001 (A)
CO (L · min <sup>-1</sup> )	4.2 ± 0.8	4.6 ± 0.9 *	4.9 ± 1.0 ***	<0.002 (A)
CVP (mmHg)	2.8 ± 2.8	6.2 ± 2.0 ***	8.0 ± 2.2 ***†	<0.001 (A)
Hb (g · dL <sup>-1</sup> )	15.5 ± 1.0	13.8 ± 1.1 *	13.2 ± 1.1 *,†	<0.001 (F)
Hct (%)	49.5 ± 2.9	44.7 ± 3.7 ***	42.7 ± 3.6 ***††	<0.001 (A)
S <sub>p</sub> O <sub>2</sub> (%)	98 ± 1	98 ± 1	99 ± 1	0.199 (F)
ETCO <sub>2</sub> (Torr)	43 ± 3	42 ± 3	42 ± 3	0.304 (A)

Data are presented as mean ± SD. P-values are expressed as (A) ANOVA or (F) Friedman.

NS-15, administration of 15 mL · kg<sup>-1</sup> of normal saline; NS-30, administration of an additional 15 mL · kg<sup>-1</sup> (total 30 mL · kg<sup>-1</sup>) of normal saline. ABP, arterial blood pressure; CBFv, cerebral blood flow velocity; CVRI, cerebral vascular resistance index; HR, heart rate; CO, cardiac output; CVP, central venous pressure; Hb, Hemoglobin concentration; Hct, Hematocrit; S<sub>p</sub>O<sub>2</sub>, arterial oxygen saturation of pulse oximetry; ETCO<sub>2</sub>, end-tidal carbon dioxide pressure.

\*,† show post hoc test with the Student-Newman-Keuls method; \*P < 0.05, compared to preinfusion; \*\*P < 0.01, compared to preinfusion; \*\*\*P < 0.001, compared to preinfusion;

†P < 0.05, compared to NS-15; ††P < 0.01, compared to NS-15.

CBF during both infusions are suggested to be increased. It has previously been reported that decreased hematocrit accompanied by hemodilution increased CBF to compensate reduced oxygen delivery.<sup>2,27</sup> Therefore, increased CO and CBF together during rapid fluid infusion are considered to provide effective hemodynamics to maintain oxygen delivery to the cerebrum. However, no rise in ICP was observed in hemodilution with normovolemia.<sup>2</sup> Therefore, hemodilution alone is not considered to be associated with changes in ICP, and the effect of hypervolemia in addition to hemodilution increases not only CBF but also ICP.

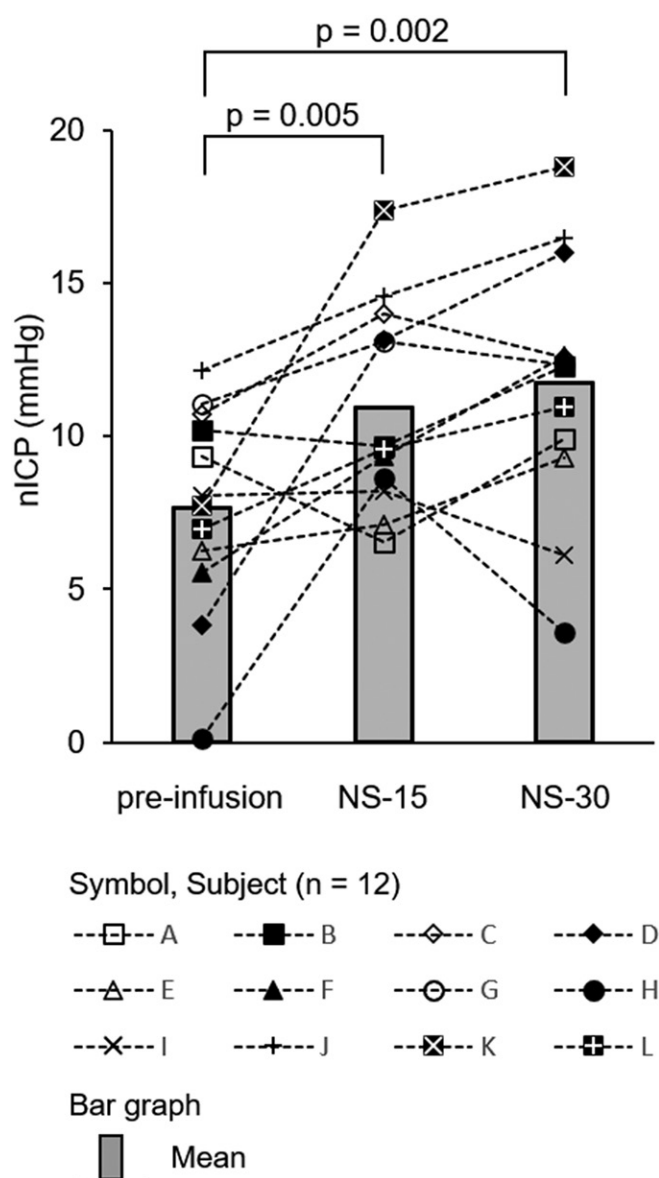
Inside the rigid compartment of the skull, the sum of the volumes of brain tissue, cerebrospinal fluid, and cerebral blood is in equilibrium with a constant steady-state pressure, according to the Monro-Kellie doctrine.<sup>18</sup> However, a temporary increase in each component would potentially affect ICP until the distribution reaches a state of equilibrium. In the present study, CVRI decreased gradually during the infusion stages, reaching a statistically significant difference at NS-30. The decreased CVRI suggests that the dilated cerebral arterioles act as resistance vessels. Therefore, decreased CVRI and increased CBFv together imply an increase in cerebral arterial blood volume involving increased cerebral arterial inflow. On the other hand, cerebral venous blood volume would also affect ICP applied with the cerebral hydrodynamic equivalent model comprising CBF pathways, as described by Czosnyka et al.<sup>4</sup> The increase in CVP observed in the present study might cause congestion in cerebral venous outflow, which would increase cerebral venous blood volume. Therefore, the rise in ICP observed in the present study was considered to be caused by both increased cerebral arterial and venous blood volume, even in a short period of time.

No differences were observed in nICP or CBFv between NS-15 and NS-30. This could be because the degree of hemodilution indicated by percent changes in hematocrit between these two infusion stages (−4%) is less than that between preinfusion and NS-15 (−10%). In the present study, the administration of 30 mL · kg<sup>-1</sup> of NS was divided into two discrete 15 mL · kg<sup>-1</sup> infusions. Therefore, the effect of a single continuous 30 mL · kg<sup>-1</sup> infusion would be stronger than the two

discrete 15 mL · kg<sup>-1</sup> (total 30 mL · kg<sup>-1</sup>) infusions in our protocol. This suggests that the degree of changes in hemoglobin concentration or blood volume derived from the time course of infusion could also affect changes in CBF and/or ICP.

Intravenous fluid administration is almost routinely applied for astronauts who return to the Earth via a Soyuz spacecraft from the International Space Station as one of the current countermeasures against postlanding syndrome.<sup>6,10</sup> The intravenous fluid administration ranged from 300 to 4000 mL,<sup>16</sup> or averaging approximately 2 L,<sup>10</sup> and are performed via medical protocol after landing and during return to Houston.<sup>10,16</sup> This information supports that the two discrete fluid administrations in the present study are included within the range of actual current intravenous administration given to postlanding astronauts. In clinical situations, rapid fluid infusion is a commonly performed intervention for patients with hemodynamics who might benefit from further fluid replacement. Appropriate fluid administration is required in both intensive care and perioperative management.<sup>1</sup> However, few studies have investigated the impact of rapid fluid infusion on ICP. The possibility that hypervolemia with hemodilution may raise ICP during fluid administration over a short period of time should be considered. After long-duration spaceflight, we found a decreased estimated value of ICP and increased CBFv in astronauts shortly after landing.<sup>10</sup> Given the fact that most of them are commonly treated with intravenous infusions, our present study results suggest the possibility that the change in ICP would be different if it is measured immediately after short-term volume loading treatment.

In the clinical setting, the rise in ICP among neurosurgical patients generally reduces CBF.<sup>4</sup> In the present study, however, CBFv increased during each infusion stage, despite the increased nICP. Therefore, the increases in both nICP and CBFv suggest that hypervolemia with hemodilution initially increased CBF and cerebral blood volume, which in turn raised ICP. On the other hand, some reports have noted that hypervolemia with hemodilution does not increase CBF in patients with subarachnoid hemorrhage.<sup>17,20</sup> The combination of hypervolemia and hemodilution for these patients is



**Fig. 2.** Changes in mean noninvasively estimated intracranial pressure (nICP). NS-15: administration of 15 mL · kg<sup>-1</sup> normal saline, NS-30: an additional administration of 15 mL · kg<sup>-1</sup> (total 30 mL · kg<sup>-1</sup>) normal saline. Each symbol shows subject individual value and the bar shows the mean for each infusion stage. The *P*-values were calculated with a post hoc test using the Student Newman-Keuls method.

usually induced by gradual fluid administration owing to the investigation into the therapeutic strategy of hypertensive, hypovolemic, and hemodilution known as triple-H. Hence, the difference in infusion speed may cause different effects on CBF and/or ICP. The fluid loading for postlanding astronauts would be slightly different from our study protocol and current fluid administration protocols and volume have been appropriate as a countermeasure against the postlanding syndrome, including reduced blood volume.<sup>6,16</sup> However, we consider that administering excess fluid over a short period should be avoided for postlanding astronauts or neurosurgical patients if it is required for ICP management.

In the present study, there was a difference in hemodynamic conditions between our participants and postlanding astronauts. Astronauts receiving short-term fluid loading are speculated to be relatively hypovolemic (~10% decrease in total blood volume) due to spaceflight effects<sup>29</sup> and may, therefore, exhibit a different response compared with that in the present study. It has been reported that roughly 2 L of body fluids were shifted upwards from the lower extremities during the initial days in space.<sup>19</sup> This translocation of body fluids to the central veins triggers regulatory responses to reduce total blood volume.<sup>8</sup> Then the lower total blood volume in microgravity alters the blood-flow distribution and takes a new set point maintained by a hormonal balance or organ metabolic adaptation.<sup>8</sup> Thus, fluid redistribution by postlanding fluid administration in astronauts would be potentially different from our participants, who were not exposed to microgravity. Also, long-duration spaceflight might increase postflight baseline ICP.<sup>15</sup> On the contrary, we have recently found that estimated ICP did not increase in the majority (≥90%) of astronauts and even significantly decreased in the nine astronauts without ocular alterations after long-duration spaceflight.<sup>10</sup> Therefore, these previous results for altered baseline ICP may also suggest a possibility that effects of fluid administration over a short period of time in astronauts who were exposed to long-duration microgravity would be different from people not exposed to microgravity.

A limitation of the present study is that we estimate the change in CBF based on CBFv assuming a constant diameter of MCA.<sup>26</sup> Previously, some studies have reported that the diameter of large arteries, including the MCA, does not change in hemodilution,<sup>9</sup> unlike the small pial arterioles (<100 μm), which showed vasoconstriction.<sup>7</sup> In addition, Larsen *et al.* demonstrated that the change in CBFv using transcranial Doppler correlated with CBF as measured by single-photon emission computed tomography within a wide range of ABP (from 50 to 120 mmHg in mean arterial pressure).<sup>14</sup> Therefore, the diameter of the MCA would be expected to remain relatively constant during hypervolemia with hemodilution. Even if the vasoconstriction occurred at distal arteries such as the pial small arterioles (<100 μm) during hypervolemia with hemodilution, the effect is considered to be small in the case of estimating nICP calculated by the algorithm using the relationship between CBFv in the MCA and ABP at the radial artery. Also, the present study was designed as a reanalysis using data from a previous experiment. No statistically significant difference in nICP was observed between NS-15 and NS-30, which could be the result of an inadequate sample size. Hence, further investigation with an adequate sample size is required to establish the effect of hypervolemia with hemodilution on ICP, including direct measure assessment.

The present study examined the change in ICP owing to hypervolemia with hemodilution induced by administration of NS over a short period of time using a mathematical analysis reflecting an intracranial hydraulic model. Hypervolemia with hemodilution induced by rapid fluid infusion appears to increase nICP as well as CBFv. Meanwhile, no changes were seen in cerebral artery compliance or PI. Therefore, the rise in

ICP estimated in the present study was considered to be induced by the increased CBFv, reflecting the increase in CBF. These findings suggest that fluid administration over a short period of time may potentially raise ICP, which is caused by increased CBF and cerebral blood volume.

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