The effect of an acute increase in central blood volume on the response of cerebral blood flow to acute hypotension

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Submitted 3 April 2015; accepted in final form 7 July 2015

ARTERIAL BLOOD PRESSURE (ABP) is an important determinant of organ blood flow. This reliance on ABP is somewhat reduced in the cerebral circulation, which displays specific cerebral autoregulatory (CA) mechanisms that maintain cerebral blood flow (CBF) relatively constant across a range of ABP (60–150 mmHg) (15). However, Lucas and colleagues (18) used a pharmacological approach and demonstrated that CBF is not stable within the CA range. This discrepancy might be due to variations between measures of static vs. dynamic CA and corresponding physiological cerebrovascular stimuli, such as sympathetic nerve activity (25, 54) or cardiac output (23), for example. CA is evaluated by measuring the relative response of CBF to a steady-state (static method) or rapid change in blood pressure (dynamic method) (46). These approaches are referred to as “static” and “dynamic” methods of CA, respectively. In some cases, dynamic CA may be a better index to identify cerebral vascular response/regulation to physiological stimulation, as this approach reflects the adaptation to lifelike physiological conditions, such as changes in posture.

Previous investigations (3, 6, 35–37) reported that dynamic CA is unlikely to be constant and is altered by a change in cerebral vascular condition. For example, hypercapnia-induced cerebral vasodilation attenuates dynamic CA, while hypocapnia-induced cerebral vasoconstriction enhances dynamic CA (1). This traditional finding suggests that changes in cerebral vasculature or cerebral vasomotion modify the response of CBF to a change in cerebral perfusion pressure. In addition to carbon dioxide (CO₂), other physiological factors affect cerebral circulation. Also, recent investigations have indicated that CBF control was modified by a change in systemic blood distribution during heat stress, exercise, and orthostatic stress (29, 31, 32, 39, 40). For example, orthostatic stress or heat stress decreases intracranial CBF (29, 31, 39). Ogoh et al. (23) demonstrated that the cardiac output associated with changes in central blood volume influenced the CBF. Thus it is expected that changes in central blood volume affect dynamic CA. However, in this earlier study (23), dynamic CA was unchanged by alterations in steady-state CBF and cardiac output. In contrast, dynamic CA was attenuated following cardiovascular blockade that reduced baroreflex-mediated defense of cardiac output during acute hypotension (33). These previous studies suggest that acute changes in central blood volume affect CBF and modify its dynamic regulation.

A change in ABP sometimes is accompanied by a change in central blood volume, i.e., acute body position change. However, no study has examined the interaction between an acute change in central blood volume and dynamic CBF regulation (mainly the response of CBF to change in perfusion pressure). A previous study reported that the switching off of lower body negative pressure (LBNP) causes an immediate increase in central blood volume and blood pressure, followed soon afterwards by a decrease in blood pressure (55). In the present study, we used this technique to test our hypothesis that an acute increase in central blood volume attenuates dynamic CA.

METHODS

Subjects

Nine healthy individuals [7 men and 2 women; age 26 ± 1 yr, weight 64 ± 3 kg, and height 171 ± 1 cm (means ± SE)] volunteered for the present study. Each subject provided written, informed consent after all of the potential risks and procedures were explained. All experimental procedures and protocols conformed to the Declaration of Helsinki and were approved by the Human Subjects Committee of Morinomiya University of Medical Sciences (no. 2014-073). All subjects had no known cardiovascular or pulmonary disorders, had no history of head injury, and were not taking any prescribed medication known to influence systemic or cerebrovascular function. Before the
formal experimentation, each subject was familiarized with the techniques and procedures. They were requested to abstain from caffeinated beverages for 12 h and from strenuous physical activity and alcohol for at least 24 h before the day of the experiment.

**Measurements**

All studies were performed at a room temperature between 23 and 24°C with minimal external stimuli. Heart rate was monitored using a lead II ECG (BSM-7201, Nihon- Kohden, Tokyo, Japan). Beat-to-beat ABP was measured via a tonometer placed over the left radial artery (BP-608 Evolution II; Omron-Colin, Tokyo, Japan); the output of the tonometric sensor was calibrated to the oscillometric blood pressure measured at the brachial artery (42). The middle cerebral artery (MCA) blood velocity was measured using transcranial Doppler (TCD) ultrasonography (WAKI; Atys Medical). A 2-MHz Doppler probe was placed over the temporal ultrasound window and fixed with an adjustable headband and adhesive ultrasonic gel (Tensive; Parker Laboratories). To gain an optimum Doppler signal, the position and angle of the TCD probe were first adjusted at the same depth for all subjects; optimization of the gain and power intensity of the signal was then modified accordingly for each subject. Ventilatory responses were measured breath-by-breath using a non-rebreathing open-circuit apparatus (model 8250; Hans Rudolf). The subject breathed through a face mask attached to a low-resistance one-way valve with a flow meter. The valve mechanism allowed the subject to room air or a gas mixture from a 200-liter Douglas bag containing 0.0 or 5.0% CO₂ in 40% oxygen (O₂) with nitrogen (N₂) balance. High O₂ concentrations in the inspiration gas potentially confounding (respiratory) influences of the peripheral chemoreflex (10). The total instrumental dead space was 200 ml. Respiratory and metabolic data were recorded using an automatic breath-by-breath gas analyzer that housed a differential pressure transducer, sampling tube, filter, suction pump, and mass spectrometer (ARCO2000-MET; Arcosystem, Chiba, Japan). We digitized expired flow, CO₂ and O₂ concentrations, respiratory rate, minute ventilation, end-tidal P₉ and end-tidal P₉. During each protocol, the data were recorded continuously at 200 Hz.

**Experimental Protocol**

On the experimental day, the subjects arrived at the laboratory at least 2 h after a light meal. After instrumentation, the subjects were placed in an LBNP box (supine position). The subjects performed two randomly assigned protocols: 1) thigh-cuff occlusion release; and 2) LBNP release. These protocols were repeated during normocapnia and hypercapnic conditions. Thus a total of four conditions were performed, and the tests were performed twice in each condition (cuff normocapnia control, cuff hypercapnia, LBNP normocapnia control, and LBNP hypercapnia; 4 × 2, total of 8 trials). In addition, the combined effects of hypercapnia and changes in central blood volume were studied. In the present study, hypercapnia was employed as a different dynamic CA condition (1). Each protocol was performed as follows.

**Thigh-cuff occlusion release.** This protocol started with a baseline period (5 min), followed by inflation of thigh cuffs (>220 mmHg) for 3 min, and then thigh cuffs were deflated. The leg vasodilation induced during ischemia causes a rapid but transient hypotensive stimuli upon cuff release when blood volume is rapidly translocated to the legs.

**LBNP release.** LBNP release was used to cause a large change in central blood volume (relative to the LBNP condition). To induce this effect, LBNP was applied for 2 min at −50 mmHg, levels that did not cause syncope in this group of participants. This protocol started with a baseline period (5 min), followed by LBNP of −50 mmHg for 2 min, and then LBNP was stopped.

During the interval period between experimental trials (>20 min), the subjects inspired room air. The order of the cuff and LBNP trials was randomized for each subject.

**Data Analysis**

Beat-to-beat mean arterial pressure (MAP) and MCA mean blood velocity (V_{mean}) were obtained from each waveform.

**Aortic pulse pressure.** Aortic pulse pressure (PP) was obtained by pulse-wave analysis using a Sphygmocor apparatus (version 7.01, Laborantin). The mean arterial pressure was calculated by subtracting the diastolic pressure from the systolic pressure.

### Table 1. Hemodynamic responses to thigh cuff and lower body negative pressure (<50 mmHg)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Baseline</th>
<th>Cuff</th>
<th>Peak Response</th>
<th>Post 8 s</th>
<th>Post 16 s</th>
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<tr>
<td><strong>CO₂ Time</strong></td>
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<tr>
<td><strong>Interaction</strong></td>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td><strong>HR, beat/min</strong></td>
<td>54 ± 2</td>
<td>52 ± 4</td>
<td>58 ± 3</td>
<td>64 ± 4</td>
<td>63 ± 3</td>
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<td><strong>MAP, mmHg</strong></td>
<td>84 ± 26</td>
<td>86 ± 5</td>
<td>62 ± 5</td>
<td>66 ± 6</td>
<td>78 ± 6</td>
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<tr>
<td><strong>Aortic PP</strong></td>
<td>39 ± 2</td>
<td>39 ± 2</td>
<td>39 ± 2</td>
<td>41 ± 2</td>
<td>40 ± 2</td>
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<tr>
<td><strong>PrPCO₂, ml/min</strong></td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>41 ± 1</td>
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<tr>
<td><strong>PrO₂, ml/min</strong></td>
<td>101 ± 24</td>
<td>101 ± 4</td>
<td>101 ± 4</td>
<td>100 ± 4</td>
<td>95 ± 4</td>
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<tr>
<td><strong>VCO₂, l/min</strong></td>
<td>9.8 ± 2.1</td>
<td>9.2 ± 2.4</td>
<td>10.3 ± 1.9</td>
<td>10.6 ± 2.0</td>
<td>9.8 ± 1.6</td>
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<tr>
<td><strong>RR, breaths/min</strong></td>
<td>13.5 ± 1.2</td>
<td>14.0 ± 1.3</td>
<td>14.4 ± 1.2</td>
<td>14.1 ± 1.3</td>
<td>14.2 ± 1.7</td>
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<tr>
<td><strong>MCA V_{mean}, cm/s</strong></td>
<td>73.8 ± 8.2</td>
<td>76.6 ± 7.8</td>
<td>7.8</td>
<td>65.1 ± 7.9</td>
<td>61.4 ± 2.4</td>
<td>75.2 ± 7.7</td>
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<table>
<thead>
<tr>
<th></th>
<th>Hypercapnia</th>
<th>Baseline</th>
<th>Cuff</th>
<th>Peak Response</th>
<th>Post 8 s</th>
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<td><strong>Baseline</strong></td>
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<tr>
<td><strong>HR, beat/min</strong></td>
<td>55 ± 4</td>
<td>63 ± 3</td>
<td>64 ± 3</td>
<td>56 ± 2</td>
<td>59 ± 3</td>
<td></td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>81 ± 3</td>
<td>86 ± 4</td>
<td>94 ± 5</td>
<td>81 ± 4</td>
<td>77 ± 3</td>
<td></td>
</tr>
<tr>
<td><strong>Aortic PP</strong></td>
<td>36 ± 2</td>
<td>29 ± 2*</td>
<td>40 ± 21</td>
<td>36 ± 2*</td>
<td>38 ± 2</td>
<td></td>
</tr>
<tr>
<td><strong>PrPCO₂, ml/min</strong></td>
<td>39 ± 1</td>
<td>37 ± 1</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>45 ± 2</td>
<td></td>
</tr>
<tr>
<td><strong>PrO₂, ml/min</strong></td>
<td>101 ± 24</td>
<td>106 ± 4</td>
<td>102 ± 4</td>
<td>103 ± 4</td>
<td>102 ± 4</td>
<td></td>
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<tr>
<td><strong>VCO₂, l/min</strong></td>
<td>10.9 ± 2.6</td>
<td>10.1 ± 2.4</td>
<td>16.3 ± 3.2</td>
<td>13.6 ± 2.9</td>
<td>19.0 ± 2.1</td>
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</tr>
<tr>
<td><strong>RR, breaths/min</strong></td>
<td>14.1 ± 1.1</td>
<td>13.4 ± 1.5</td>
<td>14.3 ± 1.3</td>
<td>12.3 ± 1.4</td>
<td>12.1 ± 1.6</td>
<td></td>
</tr>
<tr>
<td><strong>MCA V_{mean}, cm/s</strong></td>
<td>75.7 ± 8.0</td>
<td>72.2 ± 7.9</td>
<td>7.9</td>
<td>97.9 ± 10.1</td>
<td>69.4 ± 8.1</td>
<td>71.7 ± 8.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. LBNP, lower body negative pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; PP, pulse pressure; PrPCO₂, end-tidal PCO₂; PrO₂, end-tidal PO₂; VCO₂, ventilation; RR, respiratory rate; MCA, middle cerebral artery; V_{mean}, mean blood velocity. P < 0.05 vs. *baseline, †cuff or LBNP, ‡peak response, or §post 8 s.
AtCor Medical) from applanation tonometry-measured radial artery pressure waveforms, as previously reported (45).

Dynamic CBF response to acute hypotension. The responses of MCA $V_{\text{mean}}$ to acute changes in systemic blood pressure immediately following cuff or LBNP release were identified. Control values of MAP and MCA $V_{\text{mean}}$ were defined by calculating their averages during the 4 s immediately before thigh-cuff or LBNP release. Changes in MAP, MCA $V_{\text{mean}}$, and cerebral vascular conductance index (CVCi) during cuff or LBNP release were determined relative to their concomitant control values. At the time of 1.0–3.5 s from cuff release or peak MAP after LBNP release, the rate of change in CVCi [the rate of regulation (RoR)] is calculated as an index of dynamic CA (1).

$$\text{RoR} = \frac{\Delta \text{relative CVCi}/\Delta T}{\Delta \text{relative MAP}}$$

where $\Delta$ (relative CVCi)/$\Delta$T is the slope of the linear regression between relative CVCi and time (T), and $\Delta$relative MAP, the magnitude of the step, was calculated by subtracting control relative MAP from averaged relative MAP during the interval from 1.0 to 3.5 s from cuff release or peak MAP after LBNP release (1).

Statistics

Statistical comparison of physiological variables (time × CO$_2$) and RoR (condition × CO$_2$) were made utilizing a repeated-measures, two-way ANOVA. Also, statistical comparison of percent changes in MAP, aortic PP, and MCA $V_{\text{mean}}$ were made using a factorial ANOVA (condition × time). A Student-Newman-Keuls test was employed post hoc when interactions were significant. Statistical significance was set at $P < 0.05$, and results are presented as means ± SE. Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL).

RESULTS

Hemodynamic Responses During Thigh-Cuff Occlusion, LBNP, and Hypercapnia

The measured baseline hemodynamic data were unchanged by cuff occlusion and hypercapnia (Table 1). Similarly, the baseline hemodynamic variables were also unchanged by LBNP and hypercapnia, except for aortic PP. LBNP decreased aortic PP, but this reduction was not altered by hypercapnia.

Responses to Thigh-Cuff and LBNP Release

Thigh-cuff occlusion release. The release of the thigh cuffs elicited an acute decrease in ABP. Changes in MAP with thigh-cuff deflation were $-23.8 \pm 1.2$ mmHg (normocapnia control) and $-24.5 \pm 1.4$ mmHg (hypercapnia). These changes were transient and returned to baseline following an overshoot recovery pattern (Table 1, Figs. 1 and 2). As intended, these decreases in ABP were sufficient to evoke a transient and significant decrease in MCA $V_{\text{mean}}$. After the nadir of ABP, MAP gradually increased but remained lower than baseline levels for 16 s following cuff release. MCA $V_{\text{mean}}$ returned to the baseline level at 16 s post-cuff release. Aortic PP was well maintained at the baseline level throughout the cuff occlusion and release protocol. As a reflection of dynamic CA, changes in MCA $V_{\text{mean}}$ were smaller compared with MAP in all conditions. As expected, compared with normocapnia, hypercapnia significantly attenuated RoR, an index of dynamic CA ($0.167 \pm 0.025$ vs. $0.236 \pm 0.018$/s; $P = 0.024$, Fig. 3).

LBNP release. MAP was unchanged during LBNP but increased immediately after LBNP release ($+7.9 \pm 2.7$ and $+10.3 \pm 3.2$ mmHg; normocapnia control and hypercapnia, respectively; Figs. 1 and 2). However, this rise in MAP was transient and rapidly reversed with a decrease to nadir for several seconds ($-17.6 \pm 2.7$ and $-16.0 \pm 1.6$ mmHg at 16 s post-LBNP release; normocapnia control and hypercapnia, respectively; Fig. 1). Aortic PP decreased during LBNP, but increased significantly above baseline levels for 8 s following LBNP release (Figs. 1 and 2). MCA $V_{\text{mean}}$ followed these changes in MAP after LBNP release. Indeed, in this condition, the values of RoR at the acute hypotension phase ($1–3.5$ s after the peak MAP) induced by the LBNP release were lower than those obtained by thigh-cuff occlusion release (Fig. 3). In addition, there was no significant difference in RoR between normocapnia control ($0.112 \pm 0.039$/s) and hypercapnia ($0.096 \pm 0.017$/s, $P = 0.574$).
To identify dynamic CA, the change in MCA $V_{\text{mean}}$ was analyzed during acute changes in systemic blood pressure caused by two methods: 1) thigh-cuff occlusion release, which reduces systemic blood pressure without change in central blood volume; and 2) the release of LBNP ($-50$ mmHg), which acutely increased central blood volume (relative to the LBNP condition) and transiently increased and then decreased blood pressure relative to baseline. Each of these approaches was repeated under normocapnic and hypocapnic conditions. As expected, hypercapnia decreased the RoR obtained by thigh-cuff occlusion release protocol. In contrast, RoR was reduced by the LBNP release protocol, and this reduction was not modified further by hypercapnia. These findings suggest that cerebral vasculature is sensitive to changes in systemic ABP, but this physiological response is also affected by an acute change in systemic blood distribution.

CA is the mechanism that purportedly maintains a stable blood flow in the brain, despite changes in the ABP in the range of 60–150 mmHg (15). Traditionally, CA was assessed by the steady-state relationship between mean ABP and mean CBF. This method identifies the “static” characterization of CA (46). However, this concept of “static CA” established by the early work of Lassen (15) is questionable in humans, because this previous study identified the range of CA based on the relationships between CBF and ABP across 11 steady-state data points under several different conditions presented in different studies (21). Indeed, a recent study (18) demonstrated that CBF closely followed pharmacological-induced changes in blood pressure, even within the CA range in otherwise healthy humans, suggesting that a finite slope of the CA
plateau region does not necessarily imply a defective CA. In addition, steady-state CBF is likely influenced by other physiological factors as well as CA (23). Therefore, it may be difficult for an index of static CA to provide information of cerebral vasomotion and dynamic CBF regulation. Taken together, dynamic CA may be a better index to identify cerebral vascular response/regulation to physiological stimulation rather than “static CA”. Aaslid et al. (1) introduced an approach to assess “dynamic” response of CA by using the rapid drops in ABP caused by the release of thigh occlusion cuffs as an autoregulatory stimulus. This method addresses the rate at which the change in cerebrovascular resistance is achieved (its latency). Tiecks et al. (46) compared the two results of these two different approach in humans. They demonstrated that measurement of dynamic CA yielded similar results as static CA testing in normal anesthetized adults with intact or impaired autoregulation. For clinical purposes, however, dynamic CA likely reflects most aspects of the autoregulatory response correctly, because the rate of a CBF response is more important for maintaining homeostasis in the brain (46). Therefore, many previous studies investigated dynamic CA using metrics such as RoR, the autoregulatory index, transfer function analysis, and so on. However, the metrics used in these studies have poor convergent validity, and only select CA metrics can be used interchangeably, indicating that it is difficult to compare and validate results across studies (49). Accordingly, to compare the results regarding dynamic CA from existing literature, we need more precise metric(s) that characterize dynamic CA (48).

In the present study, we identified the significant reduction of aortic PP during LBNP and the subsequent increase in aortic PP by the removal of LBNP (Fig. 2, middle). Since left ventricular ejection is the main determinant of aortic PP in healthy young populations (38), the response of aortic PP to LBNP would be attributed to changes in venous return. Thus we believed that central blood volume could be manipulated effectively by LBNP release. In the present study, dynamic CA was attenuated by the LBNP release-induced acute increase in central blood volume (relative to the LBNP condition) with or without hypercapnia (Figs. 1 and 3). This finding indicates that the dynamic CBF response to acute hypotension is modified by an acute change in central blood volume. Therefore, systemic blood distribution is an important factor determining dynamic CBF regulation as well as steady-state CBF.

Recently, it has been established that dynamic CBF regulation is different between different cerebral arteries. For example, dynamic CA is lower in the vertebral than internal carotid arteries (39). Also, the reactivity to CO2 is lower in the vertebral artery vascular bed than internal carotid circulation, and markedly diminished in the external carotid circulation compared with that of the cerebral circulation (41). These different dynamic CBF regulation may explain different CBF responses to physiological stress (41). In addition, dynamic CA has asymmetrical responses to hypertension and hypotension (2, 50). Indeed, Tzeng et al. (50) demonstrated that dynamic CA is relatively more effective at guarding the brain from transient hypertension than hypotension. These previous findings provide the possibility that the present findings may not reflect patterns in the posterior circulation, and also during hypertensive periods.

Previous reports demonstrated that dynamic CA is changed by cardiovascular disease (7, 13, 19, 47, 51, 53) and could elevate the risk for cerebrovascular disease. However, the mechanism of impaired dynamic CA in patients with cardiovascular disease remains unclear. It may be that factors associated with cardiovascular impairment concomitantly affect dynamic CA, which appears to be sensitive to many factors. For example, dynamic CA is attenuated by hypercapnia and enhanced by hypocapnia (1). Further, Ogoh et al. (20, 28, 30) reported that hypoxia disrupts dynamic CA. In the integrated system, these chemoreflex factors may interact with autonomic arousal that also occurs during hypercapnia (44) and hypoxia (8, 12, 16). For example, dynamic CA is impaired by the pharmacological removal of autonomic neural activity using Prazosin (α1-adrenoreceptor blockade) (25), phenotolamine (α2-adrenoreceptor blockade) (14), and ganglion blockade with trimethaphan (54). Therefore, the reduction in dynamic CA upon release of LBNP in the present study may have been due to baroreflex-mediated reductions in sympathetic outflow. Overall, factors that influence cerebrovascular contractile state may be fundamental in determining dynamic CA. Specifically, factors that elicit cerebral vasodilation, such as hypoxia and hypercapnia, diminish dynamic CA. In the present study, as expected, MCA Vmean was increased immediately after LBNP release (+20~30%; Fig. 1), as shown previously (55). Ogoh et al. (23) demonstrated that cardiac output was related directly to CBF, indicating that blood volume distribution must be considered when studying CBF dynamics. A possible mechanism by which the increase in central blood volume elevated CBF but reduced dynamic CA is the concurrent effect of baroreflex-mediated inhibition of sympathetic outflow (9).

Despite the conclusions outlined above, the relationship between cardiac function, CBF, and dynamic CA remain complex and are not completely explained by the evidence provided by the present study. For example, upright posture decreases cardiac output and CBF, and also increases sympathetic nerve activity via arterial and cardiopulmonary baroreceptors. In addition, exhaustive heavy exercise also decreases CBF via hyperventilation-induced hypocapnia and increases sympathetic nerve activity (26). Each of these conditions impairs dynamic CA, although upright posture and heavy exercise cause cerebral vasoconstriction, which could cause enhanced CA as well. Also, vagal blockade of the baroreflex-mediated cardiac response to acute hypotension also attenuated dynamic CA, despite no change in steady-state CBF (33).
Thus, from the findings of these previous studies and the present study, cerebral vasomotion is unlikely associated with determining dynamic CA. These inconsistent results regarding the cerebral vasomotion may be related to the difference between “acute” and “steady-state” conditions, because these previous studies investigated dynamic CA during steady-state central hyper- or hypovolemic conditions. Indeed, change in central blood volume-induced steady-state central hypervolemia or hypovolemia condition does not alter dynamic CA (23).

Limitations

In the present study, there are technical limitations that warrant consideration. TCD measures blood flow velocity in the MCA rather than CBF. Blood velocity reflects blood flow only if the diameter of the blood vessel remains constant. Although early evidence suggested that the MCA diameter appears to change little with acute hemodynamic perturbations (11) and LBNP (43), recent evidence with high-field magnetic resonance imaging has reported MCA dilation during hypercapnia (4, 52), but this dilation with hypercapnia does appear to develop over the course of 1–2 min (5). These results suggest that the short-term nature of changes induced by thigh-cuff release and LBNP release models should have minimal effect on the relationship between MCA $V_{\text{mean}}$ and CBF. Another recent finding suggests that the decline in global CBF with hypotension induced by LBNP is influenced by arterial vasoconstriction in cerebral arteries and that TCD measures of flow velocity may underestimate changes in CBF during hypotension, with and without hypocapnia (17).

Perspective and Significance

Changes in central blood volume occur rapidly on Earth during changes in posture, with direct effects on ABP and cerebral perfusion (21, 23). However, the acute change in central blood volume modifies arterial pressure and aortic PP via arterial and cardiopulmonary baroreflexes (22, 24, 27, 34). In this study, after acute increase in central blood volume (relative to the LBNP condition), a large systemic vasodilation likely occurs via baroreflex function and, consequently, ABP decreases (Fig. 1). This phenomenon likely prevents cerebral overperfusion. In addition, our finding of the present study indicates that an acute increase in central blood volume (relative to the LBNP condition) attenuates dynamic CBF regulation. Taken together, regulation of systemic blood flow distribution, such as occurs through arterial and cardiopulmonary baroreflex control, maintains cerebral circulatory homeostasis. These results provide a potential mechanism by which cardiovascular disease attenuates dynamic CBF regulation (7, 13, 19, 47, 51, 53).

In summary, an acute increase in central blood volume (relative to the LBNP condition) attenuated dynamic CA. This finding suggests that systemic blood distribution is an important factor for determining dynamic CBF regulation.

ACKNOWLEDGMENTS

The authors appreciate the time and effort invested by the volunteers.

GRANTS

This study was supported in part by a Grant-in-Aid for Scientific Research (no. 24300237) from the Japanese Ministry of Education, Culture, Sports, and Science.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: S.O. and T.M. conception and design of research; S.O., A.H., H.N., S.U., and T.M. performed experiments; S.O., J.S., and T.M. analyzed data; S.O. and J.S. interpreted results of experiments; S.O. prepared figures; S.O. drafted manuscript; S.O., J.S., J.K.S., and T.M. edited and revised manuscript; S.O., A.H., J.S., H.N., S.U., J.K.S., and T.M. approved final version of manuscript.

REFERENCES


