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# Autonomic Ganglionic Blockade Does Not Prevent Reduction in Cerebral Blood Flow Velocity During Orthostasis in Humans

Rong Zhang, PhD; Benjamin D. Levine, MD

**Background and Purpose**—The underlying mechanisms for reductions in cerebral blood flow (CBF) during orthostasis are not completely understood. This study tested the hypothesis that sympathetic activation causes cerebral vasoconstriction leading to reductions in CBF during lower body negative pressure (LBNP).

**Methods**—CBF velocity, arterial pressure, and end-tidal CO<sub>2</sub> were measured during LBNP (−30 to −50 mm Hg) in 11 healthy subjects before and after autonomic ganglionic blockade with trimethaphan. Arterial partial pressure of CO<sub>2</sub> also was measured in a subgroup of 5 subjects. Mean arterial pressure during LBNP after blockade was maintained by infusion of phenylephrine.

**Results**—Before blockade, mean arterial pressure did not change during LBNP. However, CBF velocity was reduced in all subjects by 14% ( $P < 0.05$ ). Systolic and pulsatile (systolic–diastolic) CBF velocity were reduced by 18% and 28%, respectively, associated with significant reductions in pulse arterial pressure and end-tidal CO<sub>2</sub> (all  $P < 0.05$ ). After blockade, mean arterial pressure during LBNP was well-maintained and even increased slightly with infusion of phenylephrine. However, reductions in mean, systolic, and pulsatile CBF velocity, pulse arterial pressure, and ET-CO<sub>2</sub> were similar to those before blockade. In contrast to reductions in end-tidal CO<sub>2</sub>, arterial partial pressure of CO<sub>2</sub> did not change during LBNP.

**Conclusions**—These data, contrary to our hypothesis, demonstrate that sympathetic vasoconstriction is not the primary mechanism underlying reductions in CBF during moderate LBNP. We speculate that diminished pulse arterial pressure or pulsatile blood flow may reduce cerebral vessel wall shear stress and contribute to reductions in CBF during orthostasis through flow mediated regulatory mechanisms. (*Stroke*. 2007;38:000-000.)

**Key Words:** cerebral hemodynamics ■ orthostasis ■ sympathetic nervous system ■ transcranial Doppler

To stand upright, humans must maintain a stable cerebral blood flow (CBF) despite large hydrostatic pressure gradients and a shift of blood out of the thorax induced by gravity.<sup>1</sup> When this regulatory process fails, orthostatic intolerance or syncope may occur associated with an acute reduction in CBF. These abnormalities are especially critical for patients with autonomic dysfunction (who are unable to stabilize arterial pressure in the upright position),<sup>2,3</sup> or for healthy individuals after a period of bed rest or space flight.<sup>4</sup>

It has been shown repeatedly that CBF velocity, measured in the middle cerebral artery by transcranial Doppler, is reduced by 15% to 20% during upright standing, head-up tilt, or lower body negative pressure (LBNP).<sup>3–5</sup> Assuming that changes in CBF velocity represent changes in CBF, these observations are remarkably consistent with previous direct measurements of CBF in humans during orthostasis using traditional tracer methods.<sup>1</sup>

However, the underlying mechanisms for reductions in CBF during orthostasis are not completely understood. In

previous studies, we and others have shown that CBF velocity is reduced significantly during moderate LBNP when mean arterial pressure is well-maintained, suggestive of cerebral vasoconstriction.<sup>4,6</sup> This study tested the hypothesis that baroreflex-mediated sympathetic activation during orthostasis (required to preserve blood pressure) causes cerebral vasoconstriction leading to a reduction in CBF in humans.<sup>4,7</sup>

For this purpose, CBF velocity under steady-state conditions was measured during LBNP once before and once after autonomic ganglionic blockade using trimethaphan. Mean arterial pressure during LBNP after blockade was maintained by intravenous infusion of phenylephrine. Both of these drugs have been used frequently in the study of cerebral autoregulation in humans as well as in animals and have minimal, if any, direct effects on the cerebral blood vessels.<sup>8</sup> We hypothesized that reductions in CBF velocity and presumably blood flow, if mediated primarily by sympathetic vasoconstriction during LBNP, would be prevented by ganglionic blockade

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when mean arterial pressure was maintained by infusion of phenylephrine.

## Methods

### Subjects

Eleven healthy subjects (8 men, 3 women) with a mean age of  $30 \pm 2$  years, height of  $173 \pm 3$  cm, and weight of  $70 \pm 3$  kg participated in this study. No subject smoked or had known medical problems. Subjects were screened carefully with a medical history and a physical examination including a 12-lead ECG. All subjects signed an informed consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

### Instrumentation

For LBNP without ganglionic blockade, arterial pressure was measured noninvasively in all subjects with finger photoplethysmography (Finapres; Ohmeda). For LBNP with ganglionic blockade, noninvasive arterial pressure was measured in 8 subjects. For the other 3 subjects, arterial pressure was measured with a radial arterial catheter (Abbott Critical Care System) together with the noninvasive Finapres method to corroborate changes in arterial pressure and to measure arterial partial pressure of  $\text{CO}_2$  ( $\text{Paco}_2$ ). In an additional 3 subjects, blood samples for  $\text{Paco}_2$  were obtained with radial arterial punctures once at baseline and once during LBNP after ganglionic blockade. However, for technical reasons, arterial blood samples during LBNP could not be obtained in one subject. Thus,  $\text{Paco}_2$  from a total of 5 subjects are reported. The pressure transducers were positioned carefully at heart level. CBF velocity was measured in the middle cerebral artery using transcranial Doppler. A 2-MHz probe (Multiflow; DWL) was placed over the subject's temporal window and fixed at a constant angle with a probe holder that was custom made to fit each subject's facial bone structure.<sup>9</sup> With this method, highly reproducible measurements of CBF velocity can be obtained for repeated studies. Heart rate was monitored by ECG. Respiratory frequency and relative changes in tidal volume were measured using a piezoelectric transducer (Pneumotrace; Morro Bay). End-tidal  $\text{CO}_2$  ( $\text{ETCO}_2$ ) was measured via a nasal cannula using a mass spectrometer (Marquette Electronics).

### Protocol

All experiments were performed in the morning  $\approx 2$  hours after a light breakfast. The subjects refrained from caffeinated or alcoholic beverages at least 24 hours before the tests. For LBNP without blockade, after  $\approx 30$  minutes of supine rest, 6 minutes of baseline data were collected during spontaneous breathing. Then, LBNP was applied beginning at a level of  $-15$  mm Hg lasting for 8 minutes (2 minutes for stabilization and 6 minutes for data collection). The level of LBNP then was increased to  $-30$  mm Hg and subsequently increased by  $-10$  mm Hg until a previously determined target for reduction in mean CBF velocity by 10% to 15% from the baseline value was observed for each subject.<sup>4</sup>

After at least 2 weeks, the same level of individually determined LBNP was repeated after ganglionic blockade with intravenous infusion of trimethaphan (6 to 7 mg/min, trimethaphan camsylate; Cambridge Laboratories). The efficacy of blockade was confirmed by a Valsalva maneuver, demonstrating the absence of heart rate response despite significant reductions in arterial pressure.<sup>10</sup> After this procedure, low-dose phenylephrine was titrated carefully in each subject to maintain mean arterial pressure at the baseline level when  $-5$  or  $-10$  mm Hg LBNP was applied. Then, LBNP was increased incrementally by  $-5$  or  $-10$  mm Hg associated with an individually titrated dose of phenylephrine to stabilize mean arterial pressure until the target level of LBNP determined previously was reached. Then, data were collected under steady-state conditions. In this study, the dose of phenylephrine used to maintain mean arterial pressure at the final stage of LBNP after ganglionic blockade was  $1.3 \pm 0.5$   $\mu\text{g}/\text{kg}$  per minute (range, 0.7–2.0).

### Data Analysis

Beat-to-beat systolic, diastolic, pulse and mean arterial pressures, and CBF velocity were obtained for data processing (Multiflow; DWL). Respiratory frequency and relative changes in tidal volume were measured from continuous recording of the Pneumotrace (Figure 1). Changes in ventilation (volume per minute) were calculated as a product of respiratory frequency and tidal volume. Measurements at baseline and at the final stage of LBNP before and after ganglionic blockade were obtained for statistical analysis. Cerebrovascular resistance index was derived as mean arterial pressure divided by mean CBF velocity to reflect changes in cerebrovascular resistance.<sup>4,6</sup>

### Statistics

Two-way repeated measures ANOVA with Student-Newman post hoc tests were used to compare the differences between the measurements of baseline and during LBNP and before and after ganglionic blockade. Data are expressed as means  $\pm$  standard error. The significance level was set at  $P < 0.05$ .

## Results

Before ganglionic blockade, mean CBF velocity was reduced in all subjects by 14% during moderate LBNP ( $P < 0.05$ ;  $-30$  mm Hg for 3 subjects;  $-40$  for 7 subjects; and  $-50$  mm Hg for 1 subject). Mean arterial pressure did not change (Figure 2, Table). Consequently, cerebrovascular resistance index increased by 22% (Table). In addition, systolic and pulsatile CBF velocity were reduced by 18% and 28%, respectively, associated with a significant reduction in pulse pressure by 22% (Table). Of note, although there was no significant increase in ventilation,  $\text{ETCO}_2$  was reduced from  $40 \pm 1$  to  $35 \pm 1$  mm Hg during LBNP ( $P < 0.05$ ).

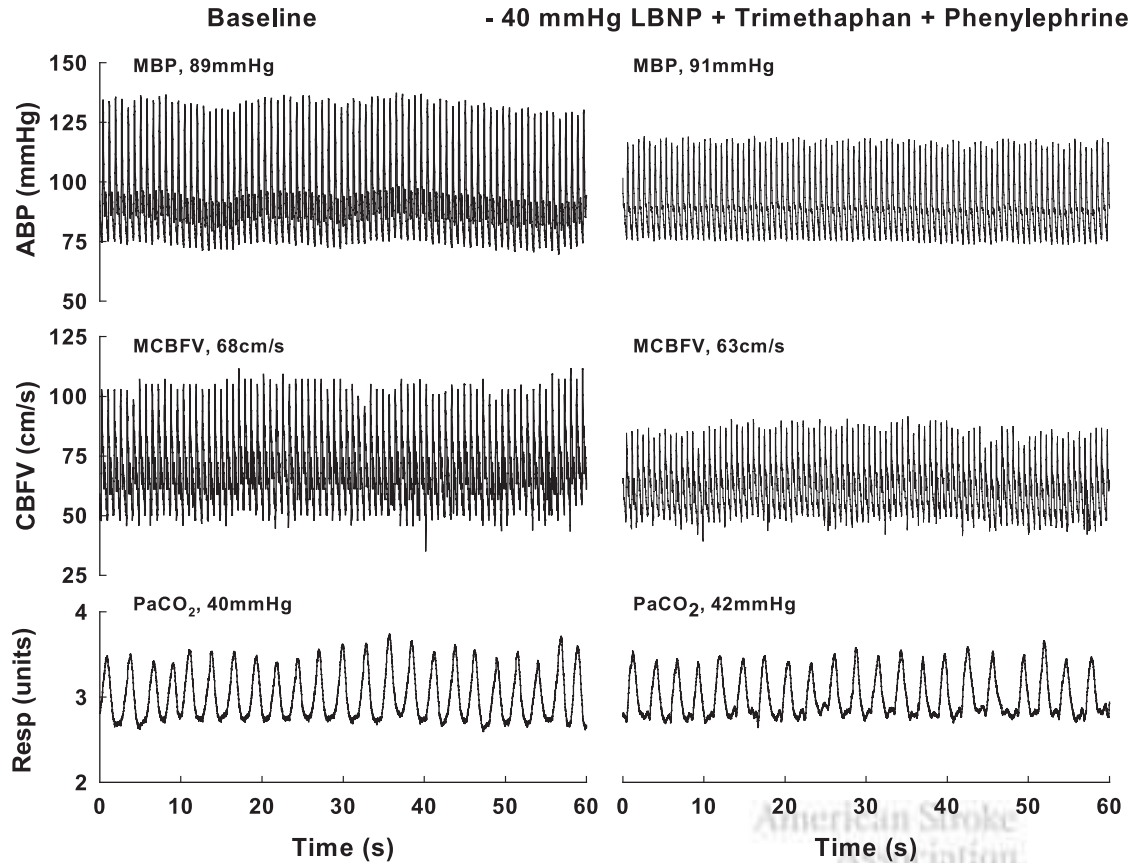
After blockade, at the same level of LBNP for each subject, CBF velocity was reduced significantly by 11% ( $P < 0.05$ ). Mean arterial pressure was maintained and even increased slightly with infusion of phenylephrine (Figures 1, 2; Table). Reductions in systolic and pulsatile CBF velocity and pulse pressure were similar to those before ganglionic blockade (Table). However, in contrast to reductions in  $\text{ETCO}_2$ ,  $\text{Paco}_2$  did not change during LBNP (Table).

## Discussion

The main finding of this study is that ganglionic blockade did not prevent the reduction in mean CBF velocity observed during moderate LBNP when mean arterial pressure was maintained by phenylephrine. Furthermore, systolic and pulsatile CBF velocity (systolic–diastolic) were reduced significantly during LBNP associated with reductions in pulse arterial pressure and these changes persisted after ganglionic blockade. Contrary to our hypothesis, these data demonstrate that changes in autonomic neural activity do not play an obligatory role in reducing CBF velocity during LBNP. We speculate that diminished pulse pressure and/or pulsatile CBF may reduce cerebral vessel wall shear stress and contribute to reductions in CBF through flow-mediated regulatory mechanisms.

### Autonomic Regulation of CBF

The cerebral vessels are richly innervated by sympathetic and parasympathetic nerves.<sup>11</sup> Data from our previous studies suggest that autonomic neural activity regulates beat-to-beat changes in CBF.<sup>10</sup> Similar to head-up tilt or upright standing,



**Figure 1.** Representative data of continuous recording of arterial blood pressure (ABP; arterial line), cerebral blood flow velocity (CBFV) and respiratory excursions at baseline and during  $-40$  mm Hg LBNP after ganglionic blockade with trimethaphan. Note that mean blood pressure (MBP) was preserved by phenylephrine infusion. However, pulse pressure and pulsatile flow were reduced substantially during LBNP.

sympathetic neural activity is augmented substantially during LBNP.<sup>7</sup> Sympathetic activation during orthostasis or stimulation of peripheral nociceptors (cold pressor test) may cause cerebral vasoconstriction in humans.<sup>4,12</sup>

However, in this study, reductions in CBF velocity and increases in cerebrovascular resistance during LBNP persisted after ganglionic blockade of autonomic neural activity. Thus, contrary to our hypothesis, these findings suggest that sympathetic vasoconstriction is not the sole mechanism underlying the reduction in CBF during LBNP.

To reach this conclusion, several factors need to be considered. First, it must be realized that ganglionic blockade inhibits not only the sympathetic but also the parasympathetic neural activity. Thus, reductions in CBF velocity during LBNP after ganglionic blockade also may be attributable to inhibition of cerebral vasodilation mediated by parasympathetic neural activity. In animal studies, intensive electrical stimulation of the cranial parasympathetic nerve increased CBF.<sup>13</sup> However, parasympathetic denervation had little effect on changes in CBF in cats under resting conditions.<sup>14</sup> In addition, parasympathetic activity most likely is reduced rather than enhanced during LBNP.<sup>7</sup> Thus, the predominant effect of ganglionic blockade on CBF should be to eliminate sympathetic activation during LBNP.

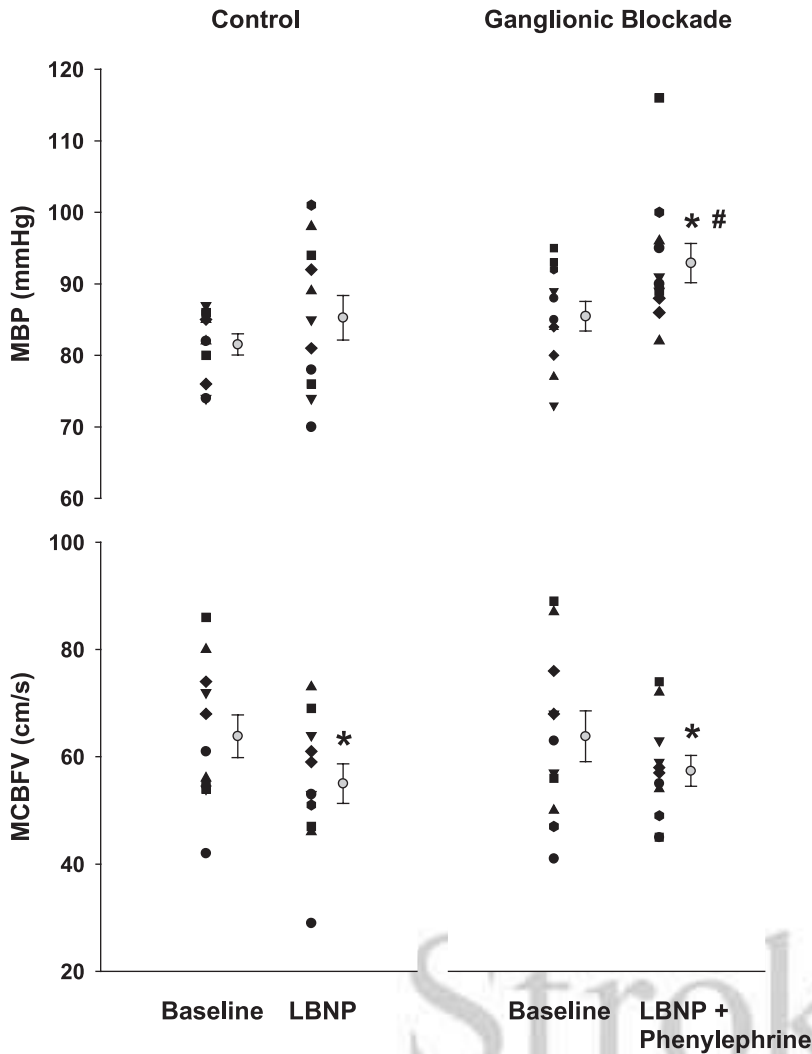
Second, although sympathetic nerve stimulation in animals attenuates the magnitude of transient changes in CBF,

sustained stimulation does not alter CBF in animals under steady-state conditions.<sup>15,16</sup> This lack of effect of sympathetic activation on CBF under steady-state conditions has been referred to as “sympathetic vasomotor escape.”<sup>16</sup> Thus, although ganglionic blockade did not prevent reductions in steady-state CBF velocity during LBNP, the possibility of sympathetic regulation of transient changes in CBF cannot be excluded.<sup>10</sup>

Finally, it should be noted that besides the extrinsic autonomic nerves, cerebral vessels are innervated by the central intrinsic nerves that arise directly from within the brain parenchyma.<sup>17</sup> Stimulation of the intrinsic nerves may cause either cerebral vasoconstriction or vasodilation depending on the specific brain regions where stimuli are applied.<sup>17</sup> Whether these intrinsic nerves were activated during LBNP and thus contributed to the reduction in CBF cannot be determined with ganglionic blockade of efferent sympathetic neural activity.

### Implications for CBF Regulation During Upright Posture

One question that deserves discussion is whether the findings during LBNP in the supine position can be extended to explain reductions in CBF velocity during head-up tilt or upright standing.<sup>5,18</sup> This uncertainty is related to how to estimate changes in cerebral perfusion pressure in humans in the upright position. For example, if the outflow hydrostatic



**Figure 2.** Mean blood pressure (MBP) and mean cerebral blood flow velocity (MCBFV) at baseline and during LBNP before and after ganglionic blockade. Arterial pressure during LBNP after blockade was maintained by phenylephrine infusion. Different symbols in the figure represent data of individual subjects. The group averaged data are presented with a vertical bar of standard error (SE). \* $P < 0.05$ , between baseline and LBNP; # $P < 0.05$ , between LBNP before and after blockade.



pressure gradient of cerebral venous and/or intracranial pressure is reduced commensurate with that of cerebral arterial pressure in the upright position, changes in mean arterial pressure at heart level may reflect changes in cerebral perfusion pressure regardless of body position.<sup>19</sup> Hence, for similar reductions in CBF in the upright position as those observed during LBNP, given a well-preserved mean arterial pressure, significant increases in cerebrovascular resistance would be expected.<sup>6,18</sup> Conceivably, these similarities in both systemic and cerebral hemodynamics would suggest that findings of the present study are applicable to the circumstances during upright standing.

Conversely, if the hydrostatic pressure gradient of cerebral venous or intracranial pressure is not reduced commensurate with that of cerebral arterial pressure in the upright position, changes in cerebral perfusion pressure then would be estimated as mean arterial pressure at heart level minus a hydrostatic pressure gradient derived from the heart-brain distance of individual subjects.<sup>20</sup> This practice has led to an estimated cerebral perfusion pressure in the upright position to be 20 to 30 mm Hg lower than that in the supine position even though mean arterial pressure was well-maintained during head-up tilt or upright standing.<sup>2,3,5</sup> Under these

circumstances, significant decreases rather than increase in cerebrovascular resistance were reported.<sup>3</sup>

These critical controversies regarding estimates of changes in cerebral perfusion pressure in the upright position cannot be resolved by this study. However, if cerebral vasodilation does occur in the upright position in response to a decline in cerebral perfusion pressure, the findings of the present study suggest that sympathetic activation is not likely to counteract this response and cause reductions in CBF.

**Arterial CO<sub>2</sub>**

Reductions in CBF during orthostasis also have been attributed to reductions in ET<sub>CO<sub>2</sub></sub> associated with the presence of respiratory instability that may be exacerbated under pathological conditions.<sup>18</sup> However, it is not clear whether the magnitude of reductions in ET<sub>CO<sub>2</sub></sub> during orthostasis truly reflects a reduction in arterial CO<sub>2</sub>.<sup>5,21</sup> Similar to reductions in ET<sub>CO<sub>2</sub></sub>, transcutaneous CO<sub>2</sub> also was reduced during head-up tilt, in support of the hypothesis that the decline in CBF during orthostasis is induced by hypocapnia.<sup>2,18,22</sup> However, recent studies with direct measurement of arterial CO<sub>2</sub> demonstrated that the magnitude of reductions in Pa<sub>CO<sub>2</sub></sub> during orthostasis was relatively small (1 to 2 mm Hg) when

**Steady-State Hemodynamics During LBNP Before and After Ganglionic Blockade**

	Control		Ganglionic Blockade	
	Baseline	LBNP	Baseline	LBNP
HR, bpm	58±3	86±4*	66±4†	86±5*
SBP, mm Hg	122±2	117±4	126±3	121±3
DBP, mm Hg	64±1	72±3*	67±2	78±3*†
PBP, mm Hg	58±2	45±2*	59±2	44±1*
MBP, mm Hg	82±1	85±3	85±2	93±3*†
SCBFV, cm/s	97±6	80±4*	97±7	78±4*
DCBFV, cm/s	43±3	41±3	44±3	43±2
PCBFV, cm/s	54±3	39±2*	54±4	35±2*†
MCBFV, cm/s	64±4	55±4*	64±5	57±3*
CVRI, mm Hg/cm per second	1.32±0.07	1.61±0.11*	1.42±0.11	1.66±0.09*
RF, breaths/min	15±2	13±1	17±2	15±1
TV, units	0.6±0.1	1.1±0.4	0.7±0.1	1.0±0.3
V <sub>E</sub> , units/min	9.0±1.4	13.4±4.3	11.4±2.1	15.0±4.1
ETCO <sub>2</sub> , mm Hg	40±1	35±1*	39±1	34±1*
Paco <sub>2</sub> , mm Hg	NA	NA	39±1	39±3

N=11, mean±SE.

LBNP indicates lower body negative pressure; CVRI, cerebrovascular resistance index; DBP, diastolic pressure; DCBFV, diastolic cerebral blood flow velocity; ETCO<sub>2</sub>, end-tidal CO<sub>2</sub>; HR, heart rate; LBNP, lower body negative pressure; MBP, mean blood pressure; MCBFV, mean cerebral blood flow velocity; NA, not applicable; Paco<sub>2</sub>, arterial CO<sub>2</sub>; PBP, pulse pressure; PCBFV, pulsatile cerebral blood flow velocity (SCBFV–DCBFV); RF, respiratory frequency; SBP, systolic pressure; SCBFV, systolic cerebral blood flow velocity; TV, relative changes in tidal volume; V<sub>E</sub>, volume of ventilation per minute.

Paco<sub>2</sub>, arterial CO<sub>2</sub> (N=5), not measured before ganglionic blockade. Blood pressure during LBNP after blockade was maintained by phenylephrine infusion.

\*P<0.05, between baseline and LBNP within the same test.

†P<0.05, between tests under same conditions.

compared with reductions in ETCO<sub>2</sub> (4–5 mm Hg).<sup>5,21</sup> In addition, when ETCO<sub>2</sub> was maintained at baseline levels, the reduction in CBF velocity persisted during head-up tilt.<sup>23</sup> These observations would suggest that reductions in CBF during orthostasis cannot be attributed solely to reductions in Paco<sub>2</sub>.

The magnitude of reduction in ETCO<sub>2</sub> observed in this study is consistent with previous studies.<sup>5,18</sup> However, in a subgroup of 5 subjects, Paco<sub>2</sub> did not change during LBNP. These data, although limited by the small number of subjects, suggest that changes in Paco<sub>2</sub> during LBNP, if any, are likely to be overestimated by changes in ETCO<sub>2</sub>, probably reflecting a ventilation/perfusion mismatch (eg, an increase in V<sub>A</sub>/Q) during orthostasis.<sup>24</sup> In a previous study, a small (1.6 mm Hg) but statistically significant reduction in Paco<sub>2</sub> has been observed during –60 mm Hg LBNP.<sup>25</sup> We have considered that given the small number of subjects in this study, such a small reduction in Paco<sub>2</sub> may not be distinguished from background noise. However, even if there was a ≈1.6 mm Hg of reduction in Paco<sub>2</sub> during LBNP, the reduction in CBF should be ≈5% because cerebral vasomotor reactivity (≈3% CBF/mm Hg CO<sub>2</sub>) does not change during LBNP.<sup>26</sup> Collec-

tively, it appears that the majority of the 11% to 14% reduction in CBF velocity during LBNP observed in this study cannot be attributed solely to reductions in Paco<sub>2</sub>.

The mechanisms for respiratory control during orthostasis are not completely understood. Ventilatory responses to changes in arterial CO<sub>2</sub> could be altered by the presence of anxiety or other emotional changes induced by the study or by interactions of the respiratory chemoreflex with other cardiovascular control mechanisms.<sup>27</sup> In previous studies, both hypoventilation and hyperventilation have been observed during moderate LBNP (–40 mm Hg) associated with reductions in ETCO<sub>2</sub>.<sup>26,28</sup> In this study, no significant changes in ventilation were observed, but there was a consistent reduction in ETCO<sub>2</sub>. Direct comparison of these data with previous studies is difficult to make because of different LBNP protocols used in these studies.<sup>26,28</sup>

**Pulse Pressure and Pulsatile CBF**

The shift of blood volume out of the thorax during orthostasis results in a decline in stroke volume by 40% to 50% and cardiac output by 20% to 40% despite increases in heart rate.<sup>1,4</sup> However, it is not clear whether these changes in stroke volume or cardiac output would have direct effects on CBF independent of changes in cerebral perfusion pressure. This question is intriguing, but counterintuitive because according to Poiseuille's law, blood flow is the quotient of perfusion pressure and vascular resistance and changes in stroke volume or cardiac output are not variables of the equation.<sup>29</sup>

However, empirical observations in patients with acute ischemic stroke and severe head injury showed that CBF in the affected brain regions correlated closely with changes in cardiac output during intravascular volume expansion alone or in combination with induced hypertension.<sup>29</sup> In addition, recent studies showed that both at rest and during exercise, increases or decreases in cardiac output with volume expansion or application of LBNP altered CBF velocity respectively in a linear fashion when mean arterial pressure and arterial CO<sub>2</sub> were kept constant.<sup>30</sup> These findings suggest the existence of a direct effect of changes in cardiac output on CBF.

The physiological mechanisms by which changes in stroke volume or cardiac output may affect CBF directly are unknown. It is plausible that altered shear stress associated with changes in pulsatile pressure and/or blood flow may modulate the steady-state pressure–flow relationship of the cerebral circulation through flow mediated regulatory mechanisms.<sup>31</sup> For example, a reduction in pulsatile flow may inhibit nitric oxide release or stimulate endothelin production from cerebrovascular endothelial cells, which in turn may result in an increase in cerebrovascular resistance and reduction in CBF.<sup>29,31</sup>

In the present study, pulse pressure and pulsatile CBF velocity were reduced significantly during LBNP both before and after ganglionic blockade, possibly reflecting reductions in stroke volume or cardiac output.<sup>4</sup> We suspect, but cannot prove, that these significant reductions in pulse pressure or pulsatile flow may induce cerebral vasoconstriction and

contribute to reductions in CBF through an important non-neural, flow-mediated regulatory mechanism.

### Study Limitations

First, as in most of studies using transcranial Doppler, the fundamental limitation of the present study is that CBF velocity rather than CBF was measured in the middle cerebral artery. Changes in CBF velocity represent changes in CBF only if the diameter of insonated cerebral arteries remains constant. Recent studies have shown that middle cerebral artery diameters in humans remain constant during moderate LBNP and that changes in CBF velocity correlated closely with directly measured changes in CBF after ganglionic blockade.<sup>8,32</sup> Therefore, it is reasonable to assume that changes in CBF velocity reflect changes in CBF in the present study.

Second, it has been shown that muscle sympathetic nerve activity is correlated positively with brain norepinephrine spillover in humans, which reflect changes in central sympathetic neural activity.<sup>33</sup> However, brain norepinephrine spillover was not measured in the present study because of the highly invasive procedures required for these measurements.<sup>33</sup> In addition, muscle sympathetic nerve activity was not measured because it has been well-established that muscle sympathetic nerve activity is eliminated completely after ganglionic blockade in humans.<sup>34</sup>

Finally, in this study, every effort was made to titrate the dose of phenylephrine infusion carefully for each subject to preserve mean arterial pressure during LBNP after ganglionic blockade. However, for subject safety, a small but significant overshoot of mean arterial pressure still occurred (Figure 2). It is possible that these increases in mean arterial pressure may have triggered a cerebrovascular myogenic response, which may have contributed to cerebral vasoconstriction during LBNP. In addition, if cerebral autoregulation was altered by ganglionic blockade of autonomic neural activity, CBF velocity might have been increased by the overshoot of arterial pressure.<sup>10</sup> If this was the case, the magnitude of the reduction in CBF velocity may have been underestimated if mean arterial pressure would have been maintained at a level similar to that during LBNP without ganglionic blockade. However, this possibility would strengthen rather than weaken the conclusion of this study.

In summary, ganglionic blockade did not prevent the reduction in CBF velocity during moderate LBNP. These data suggest that sympathetic vasoconstriction does not play an obligatory role in reducing CBF during LBNP. We speculate that diminished pulse pressure and/or pulsatile blood flow may reduce cerebral vessel wall shear stress and contribute to reductions in CBF during orthostasis through flow-mediated regulatory mechanisms.

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### Disclosures

None.

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