Cerebral autoregulation is preserved during orthostatic stress superimposed with systemic hypotension

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Guo, Hong, Nancy Tierney, Frederic Schaller, Peter B. Raven, Scott A. Smith, and Xiangrong Shi. Cerebral autoregulation is preserved during orthostatic stress superimposed with systemic hypotension. J Appl Physiol 100: 1785–1792, 2006. First published January 19, 2006; doi:10.1152/japplphysiol.00690.2005.—We sought to determine whether cerebral autoregulation (CA) is compromised during orthostatic stress superimposed with systemic hypotension. Transient systemic hypotension was produced by deflation of thigh cuffs previously inflated to suprasystolic pressure, combined with or without lower body negative pressure (LBNP). Cardiac output (CO) decreased from a baseline of 5.0 ± 0.5 l/min by −8.3 ± 1.7, −19.2 ± 2.0, and −30.6 ± 3.4% during LBNP of −15, −30, and −50 Torr, respectively. Mean arterial pressure (MAP) was maintained during LBNP, despite decreases in systolic and pulse pressures. Middle cerebral arterial blood flow velocity (V\textsubscript{MCA}) decreased significantly from a baseline of 64 ± 3 to 58 ± 4 cm/s (−9.7 ± 24%) at −50 Torr of LBNP. The reduction in V\textsubscript{MCA} was associated with a decrease in regional cerebral O\textsubscript{2} saturation. However, the percent decrease in V\textsubscript{MCA} was markedly less than that of CO. This suggests that the magnitude of the change in V\textsubscript{MCA} (an index of cerebral blood flow) is less than would be predicted, given the decrease in CO. Transient systemic hypotension decreased MAP by −21 ± 2, −24 ± 2, −28 ± 3, and −26 ± 3% at rest and during LBNP of −15, −30, and −50 Torr, respectively. Likewise, this acute hypotension resulted in decreases in V\textsubscript{MCA} of −20 ± 2, −21 ± 2, −24 ± 25, and −19 ± 2% and regional cerebral O\textsubscript{2} saturation of −5 ± 1, −6 ± 1, −6 ± 1, and −7 ± 2% at rest and during LBNP of −15, −30, and −50 Torr, respectively. Complete recovery of V\textsubscript{MCA} to baseline values following transient hypotension (ranging from 5 to 8 s) occurred significantly earlier compared with MAP (from 10 to 12 s). No subjects experienced syncope during acute hypotension. We conclude that CA is preserved during LBNP, superimposed with transient systemic hypotension, despite the decrease in V\textsubscript{MCA} associated with sustained central hypovolemia in normal healthy individuals. This preserved CA is vital for the prevention of orthostatic syncope.

blood flow velocity; cerebral oxygenation; lower body negative pressure; sympathetic nerve activity; syncope

ONE POSSIBILITY FOR THE DEVELOPMENT of orthostatic intolerance or syncope during orthostatic stress is the deterioration of cerebral autoregulatory mechanisms or cerebral underperfusion. The physiological process of cerebral autoregulation (CA) maintains cerebral blood flow (CBF) relatively constant over a wide range of cerebral perfusion pressures (CPP), extending from 60 to 150 mmHg. When arterial blood pressure (ABP) is maintained within this range of CPP, the maintenance of CBF appears to be closely related to cardiac output (CO) (17, 18, 28). In addition to CO, the maintenance of CBF is also influenced by the level of sympathetic nerve activity (45) and the partial pressure of arterial CO\textsubscript{2} (5, 32). Changes in any of these factors may affect CBF, adversely facilitating orthostatic intolerance or syncope.

Orthostatic stress is known to diminish central blood volume and CO. This results in a reflex augmentation in sympathetic nerve activity (19, 21, 36, 37) and hyperventilation, with the latter inducing significant reductions in arterial CO\textsubscript{2} (i.e., hypocapnia) (5, 32). Experimentally, orthostatic stress can be simulated by the application of lower body negative pressure (LBNP) or head-up tilt (HUT). Under these conditions, sympathoexcitiation increases vasomotor tone, maintaining ABP in the face of central hypovolemia. It has been suggested that this increase in sympathetic nerve activity may also cause cerebral vasoconstriction as middle cerebral arterial blood flow velocity (V\textsubscript{MCA}), an index of CBF, is decreased during LBNP (28, 39, 46) or HUT (4, 14, 20, 26, 31, 32). In addition, the hypocapnia induced by orthostatic stress is known to increase cerebral vasomotor tone evoking cerebral vasoconstriction (5, 32). As a result, CBF is reduced, despite the maintenance of ABP. This suggests that the CA operational range is shifted during orthostatic stress to higher CPPs, possibly as a consequence of increases in sympathetic nerve activity (28).

It has been suggested that the combined actions of increased sympathetic nerve activity (2, 14) and hypocapnia (26, 32) on the function of CA may lead to the inability to maintain CBF adequately during orthostatic stress, resulting in orthostatic intolerance or syncope. However, before the development of syncope, it has been shown that CA is well maintained during steady-state orthostatic stress in both healthy subjects and patients with recurrent vasovagal syncope (4) or neurally mediated syncope (38) under conditions in which ABP is unchanged. This finding suggests that, under such conditions, ABP remains above the lower limit of the autoregulatory range, despite a possible shift in this range to higher CPPs. However, this concept has yet to be tested under conditions in which acute systemic hypotension is manifest.

To test this concept and better define the effects of increased sympathetic nerve activity and hypocapnia on CA function, we examined the changes in V\textsubscript{MCA} that occur during graded reductions in central blood volume in the presence and absence of systemic hypotension. Specifically, we attempted to determine whether a shift in the lower limit of the cerebral autoregulatory curve to higher CPPs occurs during LBNP-induced hypotension.
sympathoexcitation and hypocapnia. We hypothesized that, if such a shift occurs during orthostatic stress, CA is compromised during acute hypotension. Theoretically, a decrease in the ability of CA to maintain CBF would contribute significantly to the development of syncope. To test this hypothesis, graded central hypovolemia was generated by the application of -0.98 and +0.98 mmHg LBNP. Subsequently, during LBNP-induced sympathoexcitation and hypocapnia, acute systemic hypotension was induced nonpharmacologically by deflating bilateral arterial thigh cuffs (previously inflated to suprasystolic pressures) after 3 min of leg ischemia (1). The results of this investigation provide novel insights into the mechanisms of orthostatic intolerance and syncope in humans.

METHODS

Subjects. Eight young men (26.1 ± 1.5 yr old, 70.5 ± 4.7 kg weight, 174 ± 3 cm height, and body mass index 23.1 ± 1.2 kg/m²) gave written consent to participate in this study approved by the Institutional Review Board for the Protection of Human Subjects at the University of North Texas Health Science Center at Fort Worth. All subjects passed a physical examination and were asymptomatic for disease before being enrolled in the study.

Measurements. During the experiment, the subject’s beat-to-beat heart rate (HR) was determined from a standard electrocardiographic lead. Systemic ABP was obtained using radial arterial tonometry (Colin model 7000 Tonometer, San Antonio, TX), a noninvasive technique that has been validated against intra-arterial blood pressure measurements within our laboratory (43) and those of others (22, 47). Stroke volume (SV) was derived from thoracic impedance measurements (four tetra polar electrodes, 3/8-in. wide Mylar tape strips, placed around the neck and lower chest; EBH100C, Biopac, Santa Barbara, CA). This method has been repeatedly validated as a reliable index of changes in central blood volume (10, 34) or SV (8, 11, 30, 40). Furthermore, our laboratory has previously validated the reliability of this technique to assess changes in the index of CO during the application of LBNP (43). CBF V_MCA was measured by transcranial Doppler (TCD) sonography using a 2-MHz probe (EZ-Dop DWL Elektronische System) placed on the left side of the head within the subject’s temporal window. The position and angle of the TCD probe was fixed to the head using a custom-made ring held by a Velcro band throughout the test. The gain and depth of the TCD signals were set ≤30% and ≤50 mm, respectively. Systemic arterial oxygen saturation (SaO₂) was determined by pulse oximeter (OXY100C, Biopac, Santa Barbara, CA). Regional cerebral oxygen saturation (S_O₂c) was determined by near-infrared (NIR) spectroscopy by using a sensor placed on right side of the forehead (Somanetics, model 4100 INVOS Cerebral Oximeter, Troy, MI) with outputting analog samples every 1 s. In this technique, two light diodes generate low-intensity NIR light at 730- and 805-nm wavelengths that is emitted into the subject’s forehead. The light penetrates the skull, dura mater, and cerebrospinal fluid, passing through the cerebral cortex. The spectral absorption of blood in the region of the cerebral cortex targeted by the light is determined by measuring the amount of light returned to two detectors positioned at distances of 3 and 4 cm from the light source (13, 16). A strong correlation (slope = 0.98 and R² = 0.96) between changes in S_O₂c and jugular venous O₂ saturation has been demonstrated previously (23). All measurements were continuously recorded by a computer and digitized online at 400 Hz. CO was determined from the product of HR and SV. Estimated total peripheral resistance (TPR) and cerebral vascular resistance (CVR) were calculated from the ratio of mean arterial pressure (MAP) to CO and the ratio of MAP to mean V_MCA, respectively. In a subset of seven subjects, fractional concentration of end-tidal CO₂ (PETCO₂) was continuously monitored via a nasal cannula by using a mass spectrometer (Perkin-Elmer, 1100 Medical Gas Analyser). Partial pressure of end-tidal CO₂ (PETCO₂) was calculated from PETCO₂ × (PB − PB̈O₂), where PB is barometric pressure, and PB̈O₂ is water vapor pressure. Respiratory frequency was calculated from the breath-by-breath analog data of PETCO₂.

Protocol. Before the experiment, subjects were familiarized with all procedures and methods of measurement to be used during testing. All experiments were performed in the morning with an ambient room temperature of 23–24°C. After instrumentation, subjects rested for a minimum of 30 min in the supine position with their lower body sealed in an LBNP box and an uninfated blood pressure cuff (wide × length: 4.5 × 30 in.). Aspen Laboratory, Englewood, CO) placed around the upper thigh of each leg. The cuffs were connected by an extension tube that was extended outside of the LBNP box, and the sealed LBNP box was tested with graded LBNP before the initiation of the experimental protocol. After the resting period, 6 min of baseline data were collected. Subsequently, LBNP of −15, −30, or −50 Torr was applied to the subjects’ lower body. After 6 min of each LBNP application, the thigh cuffs were rapidly inflated to a preset suprasystolic pressure (−200 mmHg) and maintained for 3 min. At the end of the occlusion period, both cuffs were rapidly deflated by disconnecting the extension tube (internal diameter ~8 mm) from outside of the LBNP box to produce transient systemic hypotension as a result of regional vasodilation within the limbs. Each level of LBNP was maintained for a total period of 10 min, including 6 min without cuff inflation, 3 min of thigh cuff occlusion, and 1 min of recovery after the deflation procedure. Both LBNP and cuff pressures were continuously monitored by a unit of dual-channel pressure transducers (Hewlett-Packard 78342A). All subjects tolerated and completed the LBNP and thigh cuff occlusion-deflation protocols.

Data analyses. A section of continuous data (>2 min) before the thigh cuff inflation-deflation maneuver was selected and averaged to represent the hemodynamic response to each individual level of LBNP. A second section of data collected 15 s before the cuff deflation was obtained and designated as the baseline for the hemodynamic response to the cuff inflation-deflation maneuver. The response to the cuff deflation procedure was quantified from this baseline, averaged over 15 s of data before the cuff deflation. The time to reach the nadir of response following the cuff deflation (T₁), as well as the time to recover from the nadir of response to the baseline (T₂) were identified visually and recorded. Figure 1 provides an example of the methodology used to determine T₁ and T₂. The MAP at the nadir of the mean V_MCA was selected for calculating change in CVR from the ratio of MAP to mean V_MCA at its nadir (T₁) following the cuff deflation. The CO at the nadir of the MAP was selected for estimating changes in TPR, despite a relatively constant CO following the cuff deflation. In a subset of seven subjects, 5 min of continuous data before the cuff inflation, 2 min of data during the cuff inflation, and 30 s of steady-state data after the cuff deflation were averaged from breath-by-breath end-tidal CO₂ for PETCO₂ and respiratory frequency during each level of LBNP. Results are presented as group means ± SE. On all data sets, statistics were performed using linear regression or ANOVA where appropriate. For ANOVA statistical tests, a Duncan multiple-comparison analysis for repeated measures was employed post hoc when the main effect was determined significant (i.e., P ≤ 0.05). SAS software was used for data analyses.

RESULTS

The hemodynamic responses to transient systemic hypotension in one representative subject are presented in Fig. 1. The hemodynamic responses to LBNP are presented in Table 1. LBNP significantly increased HR and decreased SV and CO. Systolic blood pressure was decreased and diastolic blood pressure was increased by LBNP. As a result, pulse pressure was narrowed during LBNP. However, MAP was maintained, despite the presence of a sustained LBNP-induced central hypovolemia, as indicated by the decreases in SV and CO. This maintenance of MAP resulted from systemic vasoconstriction.

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as reflected by significant increases in TPR. Although \( \text{SaO}_2 \) was unaffected by LBNP, \( \text{SrO}_2 \) was reduced (see Table 1). This LBNP-induced reduction in \( \text{SrO}_2 \) was significantly associated with a decrease in \( V_{MCA} \) \((R^2 = 0.992)\). Estimated CVR (ratio of \( \text{MAP} / V_{MCA} \)) was increased during LBNP. However, the magnitude of the changes in CVR (+17.2% at −50-Torr LBNP) in the cerebral circulation was less than those elicited in TPR (+53.8% at −50-Torr LBNP) within the systemic

![Fig. 1. The hemodynamic response to transient systemic hypotension induced by deflating bilateral thigh cuffs after 3 min of suprasystolic inflation in one representative subject. From top to bottom: trace of bilateral thigh cuff pressure before and after deflation; arterial blood pressure (ABP); mean arterial pressure (MAP); middle cerebral arterial blood flow velocity (\( V_{MCA} \)); mean \( V_{MCA} \); regional cerebral oxygenation (\( \text{SrO}_2 \)); systemic arterial oxygenation (\( \text{SaO}_2 \)); electrocardiogram (ECG); heart rate (HR); cardiac output (CO); and thoracic impedance (TI). Down and up arrows indicate time to reach the nadir of the response following the cuff deflation (T1) and time to completely recover from the nadir to baseline (T2), respectively. Following cuff deflation, MAP, mean \( V_{MCA} \), and \( \text{SrO}_2 \) were decreased and associated with reflex tachycardia. However, neither \( \text{SaO}_2 \) nor CO was altered during the acute bout of hypotension. bpm, Beats/min.

### Table 1. Hemodynamic responses to LBNP

<table>
<thead>
<tr>
<th>LBNP, Torr</th>
<th>HR, beats/min</th>
<th>SV, ml</th>
<th>CO, l/min</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>MAP, mmHg</th>
<th>( V_{MCA} ), cm/s</th>
<th>( \text{SrO}_2 ), %</th>
<th>( \text{SaO}_2 ), %</th>
<th>CVR, unit</th>
<th>TPR, unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62.9±3</td>
<td>79.3±5</td>
<td>5.0±0.5</td>
<td>117±2</td>
<td>63±2</td>
<td>63.9±3</td>
<td>70.5±2</td>
<td>96.2±0.6</td>
<td>1.29±0.06</td>
<td>17.2±2</td>
<td></td>
</tr>
<tr>
<td>−15</td>
<td>−2±2</td>
<td>−6±2*</td>
<td>−8±2*</td>
<td>−1±1</td>
<td>+4±2</td>
<td>+2±2</td>
<td>−3±1</td>
<td>−2±1</td>
<td>+1±1</td>
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<td>+11±2*</td>
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<td>−19±2*</td>
<td>−6±2*</td>
<td>+8±3*</td>
<td>+2±2</td>
<td>−5±2*</td>
<td>−3±1</td>
<td>+1±1</td>
<td>+7±3*</td>
<td>+26±3*</td>
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<td>−40±5*</td>
<td>−31±3*</td>
<td>−8±2*</td>
<td>+17±6*</td>
<td>+5±3</td>
<td>−10±2*</td>
<td>−5±1</td>
<td>+1±1</td>
<td>+18±8*</td>
<td>+54±9*</td>
</tr>
<tr>
<td>( P )</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.028</td>
<td>0.009</td>
<td>0.083</td>
<td>0.002</td>
<td>0.002</td>
<td>0.632</td>
<td>0.006</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as means ± SE. Data during lower body negative pressure (LBNP) are presented as a percent change from baseline. HR, heart rate; SV, stroke volume; CO, cardiac output; SBP and DBP: systolic and diastolic blood pressure, respectively; MAP, mean arterial pressure; \( V_{MCA} \), middle cerebral arterial blood flow velocity; \( \text{SrO}_2 \), regional cerebral O2 saturation; \( \text{SaO}_2 \), systemic arterial O2 saturation; CVR and TPR: estimated cerebral vascular resistance and total peripheral resistance, respectively. \( P \) values were generated using ANOVA. *Significant change from 0 LBNP.

\( P \) values: 0.001, 0.002, 0.006, 0.001
dynamic data were normalized for comparison. The identity line (slope alterations in CO during LBNP. All changes in systemic and cerebral hemo-
the time to recover to the baseline, respectively.

MAP, VMCA, and SrcO2 responses to transient systemic hypotension with or without central hypovolemia
Table 2.

was less than would be expected, given the decrease in CO as indicated by the

Fig. 2. Top: changes in cerebral vascular resistance (CVR) in relation to alterations in total peripheral resistance (TPR) during graded lower body negative pressure (LBNP). Bottom: changes in mean VMCA in relation to alterations in CO during LBNP. All changes in systemic and cerebral hemodynamic data were normalized for comparison. The identity line (slope = 1) indicates that a one-unit change on the y-axis occurs with a one-unit change on the x-axis in the same direction. By contrast, when the slope = 0, changes in the x-axis variable do not affect the y-axis variable. CVR was increased during LBNP. However, the increase in CVR was considerably less than would be expected given the increase in TPR, as indicated by the slope (0.31) of the regression characterizing their relationship. Similarly, the decrease in VMCA was less than would be expected, given the decrease in CO as indicated by the slope (0.31) of the regression characterizing their relationship.

circulation (Fig. 2, top). Consequently, the magnitude of the change in CVR was less than the change in TPR for any given level of LBNP. As a result, the change in VMCA (−9.7% at −50-Torr LBNP) for any given change in CO (−30.6% at −50-Torr LBNP) was smaller (Fig. 2, bottom).

The MAP, VMCA, and SrcO2 responses to the cuff inflation-deflation maneuver are presented in Table 2. Bilateral thigh cuff inflation with suprasystolic pressure did not significantly affect cardiovascular variables at rest or during graded LBNP. The MAP, VMCA, and SrcO2 during 3-min cuff inflation (Table 2) were statistically identical to those variables measured before cuff inflation. With or without the application of LBNP, deflation of the thigh cuffs induced a marked systemic hypotension within 2–3 s. Reductions in VMCA and SrcO2 in response to the cuff deflation were similar with or without LBNP. Although the time to reach the nadir of the MAP and VMCA responses (T1) to cuff deflation was similar during all trials, the recovery time (T2) was significantly longer for MAP than VMCA, with or without the application of LBNP. Furthermore, both T1 and T2 appeared to be consistently shorter for VMCA compared with SrcO2 during all trials. The bilateral thigh cuff inflation and deflation maneuver did not alter SaO2 at rest or during LBNP. Even though HR was significantly increased in response to the transient hypotension following cuff deflation during all trials (Fig. 1), CO was unaffected by the maneuver. With the cuff inflation, CO was 5.11 ± 0.42, 4.68 ± 0.42, 4.17 ± 0.30, and 3.29 ± 0.27 l/min during LBNP of 0, −15, −30, and −50 Torr, respectively. After the cuff deflation, CO was 5.25 ± 0.38, 4.73 ± 0.37, 4.16 ± 0.42, and 3.12 ± 0.24 l/min during LBNP of 0, −15, −30, and −50 Torr, respectively. Furthermore, these values were not statistically different from those recorded with or without LBNP before the cuff inflation-deflation maneuver (Table 1). Therefore, the systemic hypotension produced by the deflation of the bilateral thigh cuffs in all trials resulted from peripheral vasodilation. During the bilateral thigh cuff inflation, the calculated TPR was 16.3 ± 1.6, 18.9 ± 1.9, 20.8 ± 1.6, and 28.1 ± 3.0 peripheral resistance units at rest and during LBNP of −15, −30, and −50 Torr, respectively, and were similar to the TPR determined before cuff inflation (Table 1). Rapid cuff deflation following 3-min suprasystolic inflation resulted in a significant decrease in TPR (−22.7 ± 3.2, −24.7 ± 3.3, −26.5 ± 3.7, and −22.0 ± 4.0% at rest and during LBNP of −15, −30, and −50-Torr LBNP, respectively). In contrast, the magnitude of the decrease in CVR was significantly less than that of TPR in response to transient hypotension. At rest and during LBNP

Table 2. MAP, VMCA, and SrcO2 responses to transient systemic hypotension with or without central hypovolemia

<table>
<thead>
<tr>
<th>LBNP, Torr</th>
<th>Systemic MAP</th>
<th>VMCA</th>
<th>SrcO2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, %</td>
<td>Δ</td>
<td>T1, s</td>
</tr>
<tr>
<td>0</td>
<td>79 ± 3</td>
<td>−21 ± 2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>−15</td>
<td>83 ± 3</td>
<td>−24 ± 2</td>
<td>2.9 ± 1.0</td>
</tr>
<tr>
<td>−30</td>
<td>84 ± 4</td>
<td>−28 ± 3</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>−50</td>
<td>87 ± 5</td>
<td>−26 ± 3</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>P</td>
<td>0.391</td>
<td>0.149</td>
<td>0.377</td>
</tr>
</tbody>
</table>

Values are means ± SE. Baseline values represent data averaged 15 s immediately before deflation of bilateral thigh cuffs. Δ indicates the percent change in the variables at the nadir of the response to the cuff deflation procedure. T1 and T2 indicate the time to reach the nadir of the response to cuff deflation and the time to recover to the baseline, respectively. P values were generated using ANOVA. *Significant change from 0 Torr LBNP; †Significant difference in T1 or T2 compared with MAP; ‡Significant difference in T1 or T2 compared with VMCA.
of −15, −30, and −50 Torr, the percent change from baseline in CVR following the cuff deflation procedure was −0.8 ± 1.9, −4.1 ± 1.1, −5.9 ± 2.7, and −8.7 ± 2.7%, respectively. Calculated CVR values obtained 15 s before the cuff deflation maneuver (1.23 ± 0.08, 1.34 ± 0.08, 1.41 ± 0.09, and 1.49 ± 0.10 peripheral resistance units at rest and during LBNP of −15, −30, and −50 Torr, respectively) were not statistically different from those measured before thigh cuff inflation (Table 1).

\( \text{PetCO}_2 \) decreased during LBNP (\( P = 0.002 \)), and a significant hypocapnia was evident at −50 Torr (Table 3). The thigh cuff inflation-deflation maneuver appeared to change \( \text{PetCO}_2 \) (\( P = 0.025 \)). However, a post hoc analysis indicated that the difference before and after the cuff inflation or between the inflation and deflation was not statistically significant at any level of LBNP. Neither LBNP nor the cuff inflation-deflation maneuver had a significant effect on respiratory rate, suggesting that a hyperventilation-hypocapnia that occurred during LBNP was probably related to an increase in the depth of breathing.

**DISCUSSION**

Contrary to our original hypothesis, our data demonstrated that CA was preserved during transient systemic hypotension in the presence of LBNP-induced sympathoexcitation and hypocapnia. This finding suggested that no significant shift in the CA curve horizontally rightward to higher pressures occurred during steady-state LBNP (9), regardless of reductions in CO. Alternatively, it is possible that the curve was shifted to higher pressures during LBNP but that it was not relocated far enough to the right to affect normal cerebral perfusion during transient systemic hypotension. Data from the present study do suggest, however, that the CA curve was shifted vertically downward as a result of the central hypovolemia-induced reduction in CBF during LBNP. Consequently, the sustained central hypovolemia during orthostatic stress resulted in a relatively lower CBF, despite the maintenance of systemic ABP. These hypothetical shifts in the CA curve are presented in Fig. 3. Furthermore, our data indicated that an intrinsic metabolic mechanism mediated by lower \( S_{\text{aO}} \) counteracted the influence of sympathoexcitation and hypocapnia on cerebral vasomotor tone and thus CBF during static orthostatic stress. Conversely, a myogenic mechanism seemed to initiate the dynamic component of CA during rapid systemic hypotension, with or without the application of LBNP.

*Fig. 3. Hypothetical changes in the lower segment of cerebral autoregulation curves without (0 Torr) or with the graded application of LBNP of −15, −30, and −50 Torr. Dashed lines indicate the shifted range of MAP following the rapid deflation of the bilateral thigh cuffs after suprasystolic inflation. Solid circles mark the set point (i.e., CPP as determined by MAP) of the cerebral autoregulatory curve. If the threshold (or lower limit) of the cerebral autoregulatory curve is shifted to the right horizontally by sympathoexcitation and hypocapnia during graded LBNP and the set point remains constant (i.e., MAP is maintained), the systemic hypotension (indicated by dashed lines) following the cuff inflation-deflation maneuver will relocate the set point to a level below the threshold and thus compromise cerebral autoregulation, possibly facilitating orthostatic intolerance and syncope (top). This postulate was not supported by the data of the present study, since cerebral autoregulation seems operative during graded LBNP superimposed with transient systemic hypotension. Conversely, the cerebral autoregulatory curve could be progressively shifted downward vertically as a result of the hypovolemia-induced reductions in cerebral blood flow during graded levels of LBNP (bottom). As a result, the reference point (i.e., the cerebral blood flow at the set point) of the cerebral autoregulatory curve would be shifted downward in parallel with reductions in CO during LBNP, despite the maintenance of MAP. This postulate was supported by the data of the present investigation.*
Effect of static stimulus on \( V_{MCA} \). During graded LBNP, SV and CO were progressively decreased as a consequence of central hypovolemia. Despite the decrease in CO, MAP was well maintained as a result of LBNP-induced augmentations in TPR and presumably vasoconstriction. Although MAP, a surrogate measure of the mean aortic pressure that determines the set point (i.e., CPP) on the CA curve, remained within the operative cerebral autoregulatory range, \( V_{MCA} \) decreased gradually with progressive increases in LBNP (Table 1). These data were in agreement with a previous report by Levine et al. (28). The reductions in \( V_{MCA} \) were most likely due to increases in CVR mediated by LBNP-induced sympathoexcitation and hypocapnia (Table 3). However, the magnitude of the change in vasomotor tone was remarkably attenuated in the cerebral circulation compared with the systemic circulation in terms of the relative change between CVR and TPR. This finding suggests that sympathetic outflow to the cerebral vasculature is relatively weak compared with other vascular beds. There could be an intrinsic mechanism responsible for regulating \( V_{MCA} \) within the brain that opposes the increases in vasomotor tone mediated by LBNP-induced sympathoexcitation and hypocapnia. Under sustained orthostatic stress, we contend that this intrinsic mechanism is metabolic in origin. As evidence, the decreases in \( S_rO_2 \), observed during LBNP were significantly related to the reductions in \( V_{MCA} (R^2 = 0.992, \text{Table 1}) \). A decrease in \( S_rO_2 \) is representative of a reduction in cerebral \( O_2 \) delivery (15, 42), given that a subject’s metabolic rate remains unchanged under the experimental conditions used in this study. This metabolic mechanism likely mediates cerebral vasodilation, counteracting increases in cerebral vascular tone that protect the brain from underperfusion in the face of reductions in CO during sustained orthostatic stress. Alternatively, the decreases in \( S_rO_2 \) may reflect an increase in cerebral \( O_2 \) extraction facilitated by LBNP-induced reductions in CBF.

Effect of dynamic stimulus on CA. Rapid thigh cuff deflation following suprasystolic occlusion of the legs has been used extensively to elicit transient systemic hypotension (12, 29, 33, 44). In the present study, the resultant systemic hypotension appeared to be produced by a reduction in vasomotor tone, as CO remained unchanged. It should be noted that this marked systemic hypotension (decreases in MAP from \(-20\% \) to \(-28\%) \) was transient, as MAP was always completely restored to baseline values within 10–12 s. This restoration in blood pressure was most likely mediated by the arterial baroreflex (12).

Both the present and previous studies (1, 33, 44) indicate that transient systemic hypotension is accompanied by a brief yet significant decrease in \( V_{MCA} \). With or without LBNP-induced sympathoexcitation and hypocapnia, a rapid change in MAP produced a similar transient diminution in \( V_{MCA} \) during graded LBNP (see Table 2). However, \( V_{MCA} \) always recovered from an acute hypotensive stimulus more rapidly than MAP, suggesting that dynamic CA was not impaired but may have been improved by sympathoexcitation (24, 35). If the transient hypotension following the cuff inflation-deflation maneuver resulted in a drop in MAP below the threshold of the CA curve, \( V_{MCA} \) would have decreased linearly with the decrease in MAP and would have followed the same recovery time course as MAP. As this did not occur, the data suggest that dynamic CA was preserved during steady-state orthostatic stress superimposed with transient systemic hypotension. The intrinsic mechanism regulating dynamic CA during rapid, transient systemic hypotension was probably myogenic in nature. This is supported by the finding that \( V_{MCA} \) always recovered from the hypotensive challenge before the nadir of the change in \( S_rO_2 \) (see Table 2), with or without the application of LBNP. Although the monitored \( S_rO_2 \) was not pulsatile, having its sample rate selected at 1 Hz (maximal delay 1 s), and the recovery of \( V_{MCA} \) occurred 1.5 s (as \( T_1 = 1.5 \pm 0.2 \) s at LBNP of 0 Torr) after the cuff deflation, it was unlikely that an intrinsic metabolic or other extrinsic mechanism significantly contributed to dynamic CA during transient systemic hypotension.

Measurement considerations for dynamic CA. NIR spectroscopy has been adapted in several studies for monitoring cerebral regional oxygenation (\( S_rO_2 \)) and assessing cerebral perfusion during orthostatic stress (7, 15, 41, 42). In the present study, there was a significant correlation between the decreases in \( S_rO_2 \) and \( V_{MCA} \) during graded LBNP (Table 1). These data suggest that a change in \( S_rO_2 \) is a good index of the alterations in cerebral perfusion or cerebral blood volume under conditions in which metabolic rate and systemic arterial oxygenation (\( S_AO_2 \)) remain constant. Although the \( S_rO_2 \) signals were continuously monitored during the experiment, oxygenation analog data were not synchronized to the pulsatile components of the blood pressure or blood flow signals (Fig. 1). Given the analog sampling output rate was 1 Hz for \( S_rO_2 \) data, a time lag existed between \( S_rO_2 \) and \( V_{MCA} \) signal acquisition when the pulse rate was higher than 60 beats/min. This could affect interpretation of data collected to assess dynamic CA performance. However, this time lag was much less than the difference in \( T_1 \) values (i.e., time to reach the nadir of the response to transient hypotension) between \( V_{MCA} \) and \( S_rO_2 \) (Table 2). This finding suggests that, during transient systemic hypotension, in the absence of an orthostatic stress, dynamic CA is regulated by a myogenic mechanism. In contrast, graded LBNP (inducing sympathoexcitation and hypocapnia) progressively decreased \( S_rO_2 \) (indicative of a tonic metabolic stimulus) and \( V_{MCA} \) before the superimposition of the transient hypotensive stimulus. Despite these lower baseline values, the \( V_{MCA} \) recovery time (\( T_2 \)) in response to the hypotensive stimulus was not significantly different across the graded levels of LBNP and did not affect dynamic CA. Therefore, it is proposed that dynamic CA elicited by acute transient systemic hypotension is regulated primarily by a myogenic mechanism, independent of metabolic, sympathoexcitatory, and hypocapnic stimuli. The thigh cuff inflation-deflation maneuver has been commonly used as a nonpharmacological method to assess dynamic CA. However, previous studies primarily measured the downswing response (i.e., time to reach the nadir of the response to transient hypotension) to cuff release using the ratio of the changes in \( V_{MCA} \) to MAP (1, 3, 27, 33) or frequency domain analysis to determine the transfer function between MAP and \( V_{MCA} \) (44). In contrast, Lagi et al. (25) reported that the \( V_{MCA} \) upswing response (i.e., time to recover from the nadir of the response to transient hypotension) was more significant in healthy subjects than patients with autonomic failure. The present study is the first to report both the downswing (i.e., \( T_1 \)) and upswing (i.e., \( T_2 \)) responses of \( V_{MCA} \) (a surrogate measurement of CBF) and MAP following the cuff inflation-deflation maneuver. Our data document that a full recovery of \( V_{MCA} \) always precedes the recovery of MAP, with
or without LBNP. This finding suggests that dynamic CA remains functional during orthostatic stress.

Previously, studies with frequency-domain analysis suggested that variations in $V_{MCA}$ tend to be augmented along with increases in ABP variability during LBNP (44) or HUT (6, 38). Using this type of analysis, investigators have reported both a deterioration (44) and preservation (38) of dynamic CA during orthostatic stress, while others report that dynamic CA does not change until the appearance of syncope (4). Collectively, these findings suggest that dynamic CA is deteriorated only during non-steady-state orthostatic stress. The present study combined a static orthostatic stress (i.e., sustained LBNP) with a dynamic stimulus (i.e., rapid systemic hypotension). These maneuvers did not elicit orthostatic intolerance or syncope, despite progressive augmentations in cerebral vasomotor tone and diminations in $V_{MCA}$. Our data support the contention that dynamic CA, in terms of time-domain analysis, is preserved during sustained orthostatic stress with the superimposition of transient hypotension. It should be noted, however, that this study was not designed to evaluate dynamic CA function in response to transient hypertensive stimuli during LBNP-induced orthostatic stress. Further research is warranted to determine if dynamic CA is preserved under these conditions.

In conclusion, our data suggest that a significant shift in the lower limit of the CA curve to higher CPPs does not occur during LBNP-induced sympathoexcitation and hypocapnia. However, the data do suggest that the CA curve is shifted vertically downward as a result of central hypovolemia-induced reductions in CBF during LBNP. As a result, although CBF is reduced during LBNP-induced central hypovolemia, CA is preserved during transient systemic hypotension. During both sustained central hypovolemia and transient systemic hypotension, changes in $V_{MCA}$ were significantly associated with changes in CBF. This suggests that $V_{MCA}$ was directly related to cerebral $O_2$ delivery. The intrinsic mechanism regulating static CA appeared to be metabolic in nature during steady-state orthostatic stress, whereas dynamic CA appeared to be mediated by a myogenic mechanism. In the presence of LBNP-induced sympathoexcitation and hypocapnia, we conclude that CA is not compromised during the superimposition of transient systemic hypotension during sustained orthostatic stress. As a result, the preservation of CA function under these conditions may impede rather than promote orthostatic syncope.

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