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Cerebral Versus Systemic Hemodynamics During Graded Orthostatic Stress in Humans

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Background Orthostatic syncope is usually attributed to cerebral hypoperfusion secondary to systemic hemodynamic collapse. Recent research in patients with neurocardiogenic syncope has suggested that cerebral vasoconstriction may occur during orthostatic hypotension, compromising cerebral autoregulation and possibly contributing to the loss of consciousness. However, the regulation of cerebral blood flow (CBF) in such patients may be quite different from that of healthy individuals, particularly when assessed during the rapidly changing hemodynamic conditions associated with neurocardiogenic syncope. To be able to interpret the pathophysiological significance of these observations, a clear understanding of the normal responses of the cerebral circulation to orthostatic stress must be obtained, particularly in the context of the known changes in systemic and regional distributions of blood flow and vascular resistance during orthostasis. Therefore, the specific aim of this study was to examine the changes that occur in the cerebral circulation during graded reductions in central blood volume in the absence of systemic hypotension in healthy humans. We hypothesized that cerebral vasoconstriction would occur and CBF would decrease due to activation of the sympathetic nervous system. We further hypothesized, however, that the magnitude of this change would be small compared with changes in systemic or skeletal muscle vascular resistance in healthy subjects with intact autoregulation and would be unlikely to cause syncope without concomitant hypotension.

Methods and Results To test this hypothesis, we studied 13 healthy men (age, 27±7 years) during progressive lower body negative pressure (LBNP). We measured systemic flow (Q_C is cardiac output; C_2H_2 rebreathing), regional forearm flow (FBF; venous occlusion plethysmography), and blood pressure (BP; Finapres) and calculated systemic (SVR) and forearm (FVR) vascular resistances. Changes in brain blood flow were estimated from changes in the blood flow velocity in the middle cerebral artery (V_{MCA}) using transcranial Doppler. Pulsatility (systolic minus diastolic/mean velocity) normalized for systemic arterial pressure pulsatility was used as an index of distal cerebral vascular resistance. End-tidal P_ACO_2 was closely monitored during LBNP. From rest to maximal LBNP before the onset of symptoms or systemic hypotension, Q_C and FBF decreased by 29.9% and 34.4%, respectively. V_{MCA} decreased less, by 15.5% consistent with a smaller decrease in CBF. Similarly, SVR and FVR increased by 62.8% and 69.8%, respectively, whereas pulsatility increased by 17.2%, suggestive of a mild degree of small-vessel cerebral vasoconstriction. Seven of 13 subjects had presyncope during LBNP, all associated with a sudden drop in BP (29±9%). By comparison, hyperventilation alone caused greater changes in V_{MCA} (42±2%) and pulsatility but never caused presyncope. In a separate group of 3 subjects, superimposition of hyperventilation during high-level LBNP caused a further decrease in VMCA (31±7%) but no change in BP or level of consciousness.

Conclusions We conclude that cerebral vasoconstriction occurs in healthy humans during graded reductions in central blood volume caused by LBNP. However, the magnitude of this response is small compared with changes in SVR or FVR during LBNP or other stimuli known to induce cerebral vasoconstriction (hypocapnia). We speculate that this degree of cerebral vasoconstriction is not by itself sufficient to cause syncope during orthostatic stress. However, it may exacerbate the decrease in CBF associated with hypotension if hemodynamic instability develops. (***Circulation*. 1994;90:298-306.**)

Key Words • blood flow • hemodynamics • pressure • nervous system, autonomic • echocardiography, Doppler

Orthostatic hypotension resulting in syncope is a common clinical problem occurring in patients with primary or secondary autonomic dysfunction. However, it may also occur in selected groups of healthy individuals, such as endurance athletes,[1] astronauts returning from space flight,[2] or after a period of bed rest.[3] The mechanism of syncope in these individuals with an intact autonomic nervous system is not always clear and is probably multifactorial.[1,4]

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Syncope during orthostatic stress ultimately occurs because of a reduction in cerebral blood flow sufficient to cause loss of consciousness. There are two mechanisms by which this process may occur. The first and most commonly accepted hypothesis is that the fall in cerebral blood flow is secondary to systemic hemodynamic collapse, due either to an excessive decrease in central blood volume or to inadequate or inappropriate neurohumoral responses to orthostasis.[5] Alternatively, some investigators recently suggested that there may be a failure of cerebral autoregulation that may compromise cerebral blood flow during orthostatic hypotension[6] or possibly result in a centrally mediated hemodynamic collapse.[7] For example, Glaister and Miller[7] used near-infrared spectroscopy and identified a fall in oxyhemoglobin concentration associated with a reduction in brain tissue blood volume that preceded bradycardia and hypotension during presyncope induced by high

levels of lower body negative pressure (LBNP). The authors hypothesized that these changes in cerebral oxygenation may provide the trigger for the cardiovascular collapse associated with syncope during LBNP. Additional supportive data were obtained by Grubb et al,[6] who used transcranial Doppler to measure cerebral blood flow velocity during upright tilt in patients with a history of neurocardiogenic syncope and observed apparent small-vessel vasoconstriction associated with systemic hypotension. Like Glaister and Miller, they hypothesized that cerebral autoregulation may be compromised during orthostatic stress.

There are a number of limitations with these studies that reduce their impact on elucidating the pathophysiology of orthostatic intolerance. First, near-infrared spectroscopy is an indirect measure of blood flow and provides only a qualitative measure of changes in cerebral blood volume and oxygenation. Furthermore, head-up tilt produces only one level of orthostasis and thus cannot precisely define the changes in hemodynamics associated with orthostatic hypotension. Thus, the magnitude of these changes compared with other hemodynamic alterations during graded reductions in central blood volume is not clear. Moreover, the patients studied by Grubb et al[6] are not likely to reflect normal physiology in three important ways: (1) they all had a history of recurrent neurocardiogenic syncope, which may identify a group of individuals with grossly altered neurohumoral regulatory function; (2) most of them received isoproterenol during their clinical evaluation, a vasoactive drug that clearly alters systemic pulsatility and thus almost certainly alters pulsatility in the brain, making their analysis of changes in resistance difficult to interpret[8,9]; and (3) the data reported were obtained during a vasovagal episode associated with severe systemic hypotension (mean pressure, 57 mm Hg) and consequently give no clues as to the changes in neurocirculatory regulation during orthostasis without hemodynamic compromise.

Therefore, the specific aim of this study was to examine the changes that occur in the cerebral circulation during graded reductions in central blood volume in the absence of systemic hypotension in healthy humans. We hypothesized that cerebral vasoconstriction would occur and cerebral blood flow would decrease due to activation of the sympathetic nervous system even in healthy subjects with intact autoregulation. We further hypothesized, however, that the magnitude of this change would be small compared with changes in systemic or skeletal muscle vascular resistance due to the counterbalancing effect of autoregulation in the cerebral circulation and would be unlikely to contribute to orthostatic hypotension.

Methods

Subjects

Subjects included 13 healthy young male volunteers with a mean age of 27±7 years (mean±SD). Seven of the subjects were endurance athletes ($\dot{V}O_2max$, 68±7 $mL \cdot kg^{-1} \cdot min^{-1}$), and 6 were sedentary students ($\dot{V}O_2max$, 41±4 $mL \cdot kg^{-1} \cdot min^{-1}$) whose characteristics have been reported previously.[4] All subjects provided informed consent to a protocol previously approved by the University of Texas institutional research review committee.

Orthostatic Stress

We used progressive lower body negative pressure (LBNP) to decrease central blood volume in a graded fashion and facilitate physiological evaluation during controlled orthostatic stress. The subjects were placed in a cylindrical metal LBNP tank sealed at the level of the iliac crests. Suction was provided by a vacuum pump and controlled with a regulator calibrated against a mercury manometer. After at least a 30-minute baseline period of quiet rest, the magnitude of the suction was increased in a stepwise fashion according to the following protocol: −15 mm Hg×15 minutes, −30 mm Hg×5 minutes, −40 mm Hg×15 minutes, and −55 mm Hg (the maximum suction generated by our device)×30 minutes. This protocol has been used in previous studies of cardiovascular regulation following head-down tilt[10] and space flight and allows data collection at both high and low levels of LBNP as well as a test of maximal tolerance. LBNP was discontinued if the subject developed signs or symptoms of presyncope: sudden onset of nausea, sweating, lightheadedness, bradycardia, or hypotension on completion of the protocol.

In a separate group of 3 subjects, the same LBNP protocol was performed, and the subjects were asked to hyperventilate sufficient to reduce P_ACO_2 to 20 mm Hg at the end of each stage. This protocol was designed to test the specific hypothesis that additional cerebral vasoconstriction during LBNP would not affect blood pressure regulation or level of consciousness.

Hemodynamic Monitoring

Heart rate was monitored continuously by ECG, and arterial pressure was also measured continuously at the finger using photoplethysmography (Finapres, Ohmeda). Indirect blood pressure was measured every 1 to 2 minutes by recording cuff pressure and the Korotkoff sounds at the brachial artery (Narco Bio-systems).

Systemic blood flow or cardiac output was measured with a standard inert gas rebreathing technique using acetylene as the soluble and helium as the insoluble gas. Adequate mixing of rebreathing gas in the lung was confirmed by a constant level of helium in all cases. This technique has been described previously[11] and has been validated against both green dye[11] and thermodilution[12] methods in healthy subjects and in patients with significant cardiopulmonary disease. Mean arterial pressure obtained during the rebreathing was divided by cardiac output to calculate systemic vascular resistance.

Blood flow was assessed at the arm and in the brain. Forearm blood flow was measured using venous occlusion plethysmography. An air-filled, double-rubber latex cuff was connected to a pressure transducer and placed over the largest part of the subject's dominant forearm. Cuff pressure was displayed on an ink jet recorder (Mingograph) and blood flow was estimated from the rate of increase of cuff pressure during venous occlusion. Occlusion cuffs were placed at the wrist and above the elbow. After inflation of the distal cuff to exclude hand blood flow, two or three flow measurements were made at a proximal cuff pressure of 50 mm Hg. These measurements were then averaged and divided into indirect mean blood pressure, recorded simultaneously with flow, to calculate forearm vascular resistance at rest and each level of LBNP.

In the brain, we used transcranial Doppler to measure blood flow velocity in the middle cerebral artery (MCA).[13] This technique allows noninvasive and repeatable estimates of changes in cerebral blood flow on a beat-to-beat basis.[14] A 2-MHz Doppler probe (TC2-64, Eden) was placed over a temporal window and fixed at a constant angle and position with an adjustable headband to obtain signals from the MCA according to standard techniques.[13,15] Systolic, diastolic, and mean velocities were generated by computer and averaged over four or five cardiac intervals. Signals were recorded every 30 seconds, and the final 3 minutes of each level of LBNP was considered as a steady state for statistical comparison. Because not all subjects tolerated all levels of LBNP and because during presyncope both systemic and regional hemodynamic variables were changing rapidly, making precise identification of MCA blood flow velocity difficult, the maximal values

Level of Lower Body Negative Pressure

	Level of LBNP, mm Hg				
	Rest	−15	−30	−40	−55
Group (n=13)					
HR, bpm	58±3	63±3*	68±4*	76±4*	90±5*
BP, mm Hg	82±2	83±3	83±3	84±3	88±3
SV, mL	98±5	90±5	73±6*	55±4*	39±4*
Fainters (n=7)					
HR, bpm	55±4	59±4	67±3*	76±5*	84±6*
BP, mm Hg	80±3	82±3	80±3	84±7	80±6
SV, mL	104±7	97±6	76±7*	55±6*	32±9*
Nonfainters (n=6)					
HR, bpm	62±6	67±6	70±7	77±8*	93±7*
BP, mm Hg	85±3	85±2	85±4	85±3	93±2*
SV, mL	90±8	83±7	71±10*	55±7*	41±5*

LBNP indicates lower body negative pressure; HR, heart rate; BP, mean blood pressure; and SV, stroke volume. Values are mean±SEM; *$P<.05$.

reported represent values obtained immediately before presyncope.

Gosling pulsatility (systolic minus diastolic/mean velocity) was used as an index of vascular resistance.[16] This ratio describes the shape of the blood velocity to time waveform. It represents the proportion of flow energy that is pulsatile and is related to the elasticity of the vascular system; changes in pulsatility reflect changes in cerebral small-vessel resistance.[16] For example, during cerebral vasoconstriction, the diastolic velocity is decreased, resulting in a low mean velocity and a high pulsatility; conversely, during vasodilitation diastolic velocity is increased, mean velocity is high, and pulsatility is low.[13,15,17] The details of the mathematical calculations regarding this parameter can be found in the appendix to the original report by Gosling (Woodcock et al[16]). Because pulsatility in the brain is affected importantly by systemic pulse pressure,[8,9] we correct for this effect by dividing the velocity pulsatility by arterial pressure pulsatility to derive a pulsatility ratio.[18]

During LBNP, electromyographic (EMG) signals of the rectus abdominus, rectus femoris, and vastus medialis were monitored continuously to ensure that straining maneuvers or muscle contraction were not being performed.[19] End-tidal CO_2 was also monitored using a mass spectrometer (Perkin-Elmer MGA 1100) or infrared CO_2 monitor (Nelcor).

Statistical Analysis

Changes in hemodynamic variables from rest to maximal tolerated LBNP were compared using a paired t test. The subjects were also divided into those who did and those who did not have presyncopal reactions during LBNP and the time course of the hemodynamic changes were compared using two-way ANOVA with Scheffé's post-hoc test for multiple comparisons. Statistics were performed using a PC-based software program (ABSTAT, AndersonBell).

Results

Orthostatic Tolerance

Seven of the 13 subjects (6 athletes and 1 nonathlete) had presyncopal reactions during LBNP, always associated with a sudden fall in both blood pressure (29±9%) and heart rate. The cumulative stress index for all subjects, calculated as the sum of the products of the duration of LBNP and the magnitude of the negative pressure at each level (mm Hg×min), was 1886±957 (mean±SD). This index is specific to this LBNP protocol and may not be comparable to stress indexes derived during other protocols. One subject had presyncope at −30 mm Hg, four had presyncope at −40 mm Hg, and two had it at −55 mm Hg. Steady-state values for heart rate, blood pressure, and stroke volume during LBNP are reported in the Table. We have previously reported that LBNP of −15 and −30 mm Hg in these subjects resulted in a fall in pulmonary capillary wedge pressure from 10.3±0.7 to 6.9±0.6 to 4.2±0.7 mm Hg from baseline (supine) through −15 and −30 mm Hg LBNP, respectively.[4]

Regional and Systemic Blood Flow

Representative Doppler and arterial pressure (finger) waveforms from one subject at rest, during maximal LBNP immediately before the onset of presyncope, and for comparison purposes during moderate hyperventilation are shown in Fig 1. Mean arterial pressure did not change significantly from rest to maximal LBNP. MCA blood flow velocity decreased at maximal LBNP but decreased by more than twice as much during hyperventilation (P_ACO_2, 20 mm Hg). Similarly, the pulsatility ratio increased during LBNP, suggestive of small-vessel vasoconstriction. However, this increase was almost fourfold greater during hyperventilation.

For all subjects, mean MCA blood flow velocity decreased from rest to maximal LBNP by 15.5±5% ($P<.05$), consistent with a reduction in cerebral blood flow (Fig 2). This decrease was approximately half the 29.9% decrease in cardiac output ($P<.05$) and the 34.4% decrease in forearm blood flow ($P<.05$). Simultaneously, there was a 17.2±10% increase in pulsatility ratio ($P<.05$), suggestive of downstream cerebral vasoconstriction, associated with increases in systemic and forearm vascular resistances of 62.8% and 69.8%, respectively (Fig 3). For technical reasons, primarily patient safety, and to facilitate comparison between subjects, not all of whom experienced presyncope, the maximal values of all hemodynamic variables are re-

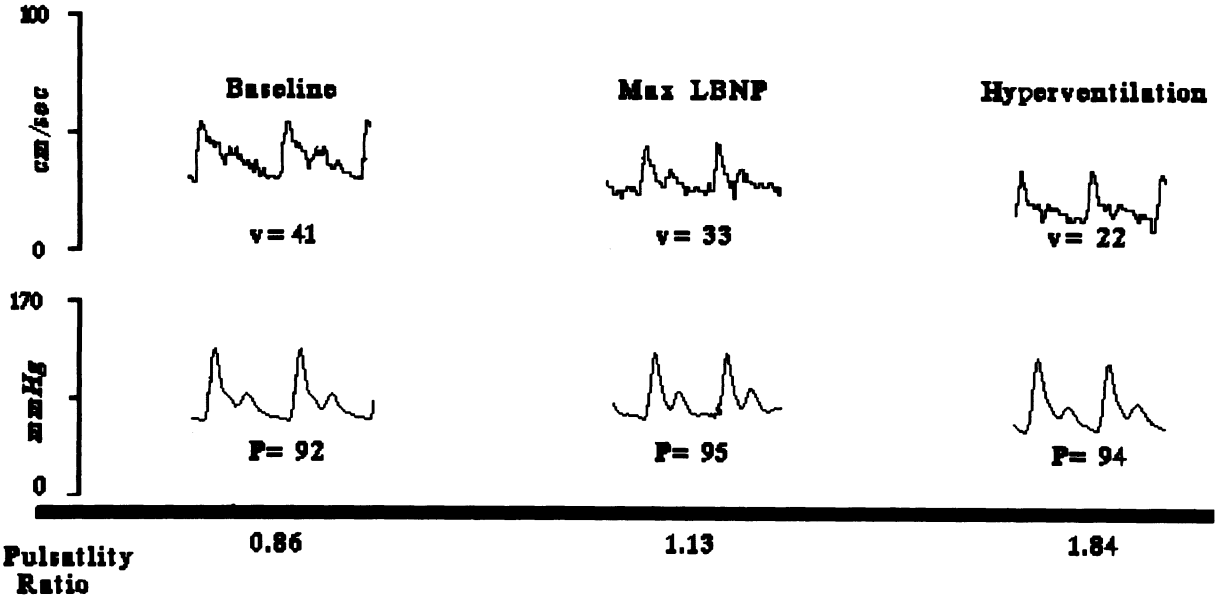

FIG 1. Representative Doppler and arterial pressure (finger) waveforms from one subject at rest, during maximal lower body negative pressure (LBNP) immediately before the onset of presyncope, and, for comparison, during moderate hyperventilation. The pulsatility ratio as described in the text is shown under each condition. Velocity waveforms are generated by computer and acquired together with the pressure waveform. v indicates mean velocity; P, mean arterial pressure.

ported as the 30-second period immediately before the onset of presyncope.

During hyperventilation at baseline, MCA velocity decreased by 43±2% associated with a 6 mm Hg decrease in mean arterial pressure. This degree of vasoconstriction caused by hyperventilation alone never caused presyncope. In addition, when hyperventilation was performed to the same end-tidal CO_2 (20 mm Hg) during LBNP, MCA velocity decreased by an additional 31±7% consistent with prominent cerebral vasoconstriction, associated with a similar 4 mm Hg decrease in mean arterial pressure. Of note, the minimal MCA velocity was the same during hyperventilation both at rest and during LBNP (31±7 versus 33±5 cm/s, respectively). This maneuver during LBNP did not initiate hemodynamic instability or alter the level of consciousness in any subject.

Fainters Versus Nonfainters

Both groups of subjects—those who had presyncopal reactions (fainters) and those who did not (nonfainters)—had significant reductions in cardiac output during LBNP, although the fainters had a decrease earlier in the protocol at a lower level of LBNP (−30 mm Hg) than the nonfainters (−40 mm Hg) (Fig 4). Similarly, there was a significant decrease in MCA blood flow velocity in both the fainters and nonfainters, with the decrease occurring earlier in the fainters (−40 versus −50 mm Hg). Forearm blood flow decreased significantly in the nonfainters. Because of subject dropout at lower levels of LBNP, there was no statistically significant decrease in forearm blood flow at any given level of LBNP in the fainters. However, the maximal decrease from rest was not different between fainters and nonfainters for any systemic or regional flow parameter.

Coincident with the decrease in flow, there was a significant increase in systemic vascular resistance in

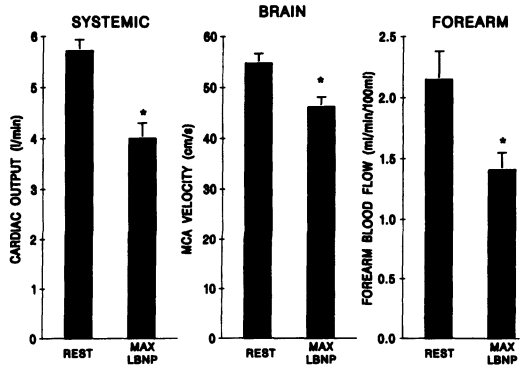

FIG 2. Mean±SEM values for systemic blood flow (cardiac output, acetylene rebreathing), brain blood flow velocity (transcranial Doppler), and forearm blood flow (venous occlusion plethysmography) at rest and during maximal lower body negative pressure for all subjects; *P<.05 compared with rest. n=13.

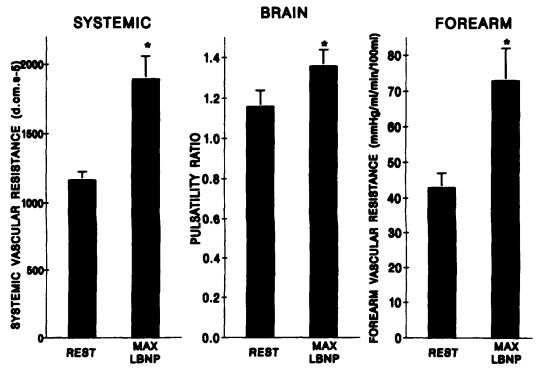

FIG 3. Mean±SEM values for systemic vascular resistance, Doppler pulsatility ratio as an estimate of changes in cerebral vascular resistance, and forearm vascular resistance at rest and during maximal lower body negative pressure for all subjects; *P<.05 compared with rest. n=13.

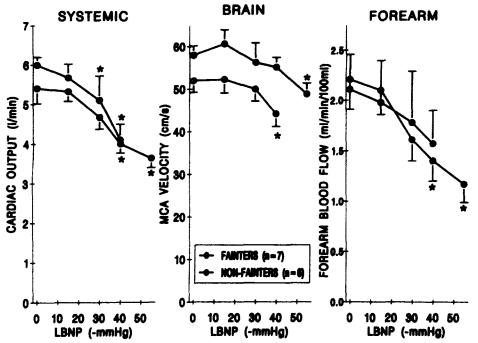

FIG 4. Time course of changes in systemic blood flow (cardiac output, acetylene rebreathing), brain blood flow velocity (transcranial Doppler), and forearm blood flow (venous occlusion plethysmography) during progressive lower body negative pressure (LBNP). Open circles represent subjects who developed presyncopal reactions during LBNP (fainters); closed circles represent those who tolerated the full protocol (nonfainters); *$P<.05$ compared with rest.

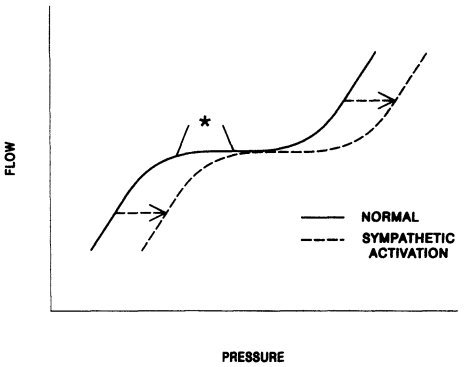

FIG 6. Hypothetical autoregulatory curves relating arterial pressure to cerebral blood flow, under normal conditions (solid line), and during sympathetic activation during LBNP (dashed line); *the lower limit of autoregulation, which, during sympathetic activation, is likely to be shifted to the right. This shift may compromise cerebral autoregulation during hypotension induced by orthostatic stress, contributing to symptoms of presyncope.

both groups, with the increase occurring earlier in the fainters (−30 mm Hg) than in the nonfainters (−40 mm Hg) (Fig 6). The fainters had an increase in pulsatility ratio consistent with downstream cerebral vasoconstriction that could not be detected in the nonfainters. Forearm vascular resistance increased significantly in the nonfainters. As with forearm blood flow, because of subject dropout at lower levels of LBNP, this increase could not be demonstrated statistically in the fainters at specific levels of LBNP, although the maximal difference from rest was not statistically different for any parameter of vascular resistance between groups.

Discussion

This study provides new information about cardiovascular regulation during orthostatic stress in two important ways. First of all, cerebral blood flow velocity decreased during graded LBNP in healthy humans before the onset of hypotension, associated with an increase in pulsatility suggestive of increased cerebral vascular resistance and small-vessel vasoconstriction. This finding is contrary to what might be predicted from the traditional concept of autoregulation, which would anticipate a compensatory vasodilitation to maintain cerebral blood flow constant. Furthermore, in subjects who were prone to syncope during LBNP, these changes in cerebral hemodynamics occurred at lower levels of LBNP than those subjects who regulated arterial blood pressure more successfully. However, these changes in the brain were relatively small compared with the changes in systemic flow and resistance or the changes in flow and resistance observed in the forearm. In addition, the reduction in blood flow velocity and the increase in pulsatility during LBNP were much less than those observed during hyperventilation, which never caused syncope; moreover, further vasoconstriction induced by hyperventilation during LBNP never affected blood pressure or level of consciousness. Thus, the degree of cerebral vasoconstriction that normally occurs during LBNP is unlikely to cause a primary failure of cerebral autoregulation or be the precipitating stimulus for systemic hemodynamic collapse.

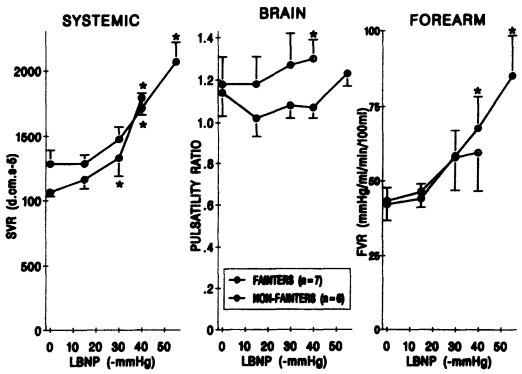

FIG 5. Time course of changes in systemic vascular resistance, pulsatility ratio, and forearm vascular resistance during progressive lower body negative pressure (LBNP). Open circles represent subjects who developed presyncopal reactions during LBNP (fainters); closed circles represent those who tolerated the full protocol (nonfainters); *$P<.05$ compared with rest.

Validity of Doppler Method

Cerebral blood flow is particularly difficult to measure because of its complex vascular supply and control mechanisms, which result in a heterogeneous regional distribution of flow.[20] The present study of cerebral blood flow in humans required a technique that is safe and noninvasive and allowed repeatable estimates of changes in global flow on a beat-to-beat basis. To meet these requirements, we used the transcranial Doppler technology developed by Aaslid et al[13] that takes advantage of the ability of ultrasound at relatively low frequencies (2 MHz) to penetrate the skull. The MCA is ideally suited for this technique because its axis makes a relatively small angle with that of the Doppler beam, optimizing the opportunity for obtaining true maximum velocities. Furthermore, this angle remains constant throughout a study, thus ensuring that the Doppler signals are proportional to true blood velocity. Because of its safety, ease of use, and ability to monitor rapid changes in global cerebral blood flow from velocity, transcranial Doppler has become a standard clinical tool in the evaluation of diseases of the cerebral circulation.[15,17]

However, it is important to emphasize that velocity is not necessarily equal to flow. The relation between velocity and flow depends on the area of the vessel being insonated according to the following equation: flow (mL/min)=velocity (cm/min)×area (cm^2).[17] When both area and velocity are precisely known, for example, by placing ultrasonic crystals directly under a pial artery, the Doppler technique has been validated in animal models as an accurate method for measuring regional cerebral blood flow compared with the use of radioactive microspheres.[21] In intact animals, including humans, the diameter of the MCA may be more difficult to quantify. Despite this difficulty, both angiographic studies[22,23] and direct visualization of the MCA during surgery[24] have suggested that during a variety of stimuli known to affect cerebral blood flow, the diameter of the MCA changes minimally (<4.0%). Thus, in humans, despite our inability to measure flow directly, it is likely that changes in blood flow velocity measured by Doppler are directly proportional to changes in flow. This hypothesis has been elegantly tested by Lindegaard et al,[14] who compared carotid flow using an electromagnetic flow probe around the carotid artery to blood flow velocity in the MCA with transcranial Doppler. When these two techniques were compared in more than 500 patient observations, there was a close correlation (r^2=.90) between carotid flow and MCA velocity. The slope was virtually the line of identity, with a standard error of the estimate of 5.3%.[14] We believe, therefore, that transcranial Doppler is an appropriate method for identifying rapid changes in global cerebral blood flow during LBNP in human subjects.

It is also important to emphasize that this technique only provides a measure of global flow to the brain through the MCA, which supplies both the cortex and the brainstem. It is possible that regional changes in cerebral blood flow, particularly to the areas of the brainstem modulating autonomic neural control, might be different between LBNP or hyperventilation, thus obscuring an important qualitative difference between the two stimuli. However, we are not aware of any systemic stimulus such as hypovolemia (LBNP) or hypocapnia (hyperventilation) that has been reported to cause focal ischemia in the human brain out of proportion to changes in the large vessels such as the MCA. Some guidance can be taken from animal studies. For example, Mueller et al[25] have used radioactive microspheres to examine regional brain blood flow during a variety of stimuli. Hypocapnia did not redistribute cerebral blood flow and resulted in vasoconstriction to a similar degree in all vascular regions.[25] Based on these data, it is likely that the reduction in MCA blood flow velocity observed in our studies during hyperventilation represents an accurate estimation of the reduction in cerebral blood flow caused by the metabolic stimulus of hypocapnia to all regions of the brain. Moreover, Mueller et al[25] also showed that during hemorrhagic hypotension, there was relative preservation of blood flow to the brainstem and cerebral gray matter that was independent of the effect of the sympathetic nervous system. This observation argues against the possibility in our studies that important physiological reductions in blood flow to either cortical or brainstem regions might have been missed by monitoring global cerebral blood flow during LBNP.

Reduction in Cerebral Blood Flow During LBNP

Because of this difficulty with methods, there is surprisingly little information in the literature regarding changes in cerebral blood flow during orthostatic stress such as LBNP. Two early human studies used the Kety-Schmidt nitrous oxide technique to measure cerebral blood flow during head-up tilt.[26,27] Shenkin et al[27] showed no change in cerebral blood flow with a modest degree of tilt to 20°C. However, Scheinberg and Stead[26] were able to demonstrate a reduction in cerebral blood flow of 20.5% when the angle of tilt was increased to 65°. Waldemar et al[28] used ^{133}Xe inhalation tomography and did not find any change in cerebral blood flow during low-level LBNP up to a maximum of −30 mm Hg. With higher levels of LBNP (−60 mm Hg), Wolthuis et al[29] found a small reduction (approximately 7%) in cerebral blood volume as measured by ^{131}I activity. More recently, Glaister and Miller[7] demonstrated a reduction in cerebral blood volume and oxygen sufficiency using near-infrared spectroscopy during presyncopal LBNP up to 90 mm Hg. These investigators observed that a reduction in oxyhemoglobin and cytochrome C oxidase occurred only at presyncopal levels of LBNP and preceded hemodynamic collapse by approximately 20 seconds. They argued that this apparent reduction in cerebral oxygenation might be a "trigger" for cardiovascular decompensation mediated through central neurohumoral mechanisms. To our knowledge, there are no other published data supporting this hypothesis. Moreover, this study is difficult to interpret because near-infrared spectroscopy is qualitative rather than quantitative and does not provide a measure of the magnitude of the response with respect to cerebral oxygenation or hemodynamics. Finally, Lightfoot et al[30] were unable to confirm a decrease in global cerebral function as measured by somatosensory evoked potentials during a similar degree of presyncopal LBNP.

Finally, Grubb et al[6] have used transcranial Doppler to study patients with recurrent unexplained syncope. This patient population is not likely to be representative of the normal human physiological response to orthostasis, however, as confirmed by the absence of any change in cerebral blood flow velocity during hyperventilation or hypoventilation in their subjects. These patients thus appear to have abnormal cerebral metabolic regulation of blood flow. The primary observation made by the authors in this study was a reduction in mean velocity during severe systemic hypotension occurring during tilt-induced syncope.[6] It is no surprise that brain blood flow decreases during the severe systemic hypotension such as observed in their studies, which likely falls below the lower limit of autoregulation. What is surprising about their results is the increase in pulsatility of the Doppler waveforms, which the authors argue is a result of paradoxical cerebral vasoconstriction. However, it is not clear whether pulsatility accurately reflects cerebral vascular resistance in the setting of the rapid changes in hemodynamics occurring during neurocardiogenic syncope. Moreover, many of their patients received infusions of isoproterenol during their clinical testing protocol, which further complicates the interpretation of changes in pulsatility. Isoproterenol, a selective β_1-adrenergic agonist, increases cardiac contractility, decreases systemic vascular resistance, in-

creases systemic pulse pressure, and therefore markedly changes the dynamics of ventriculovascular coupling. Recent mathematical models have emphasized the importance of the nature of systemic pulsatile flow for the characteristics of pulsatile flow and velocity in downstream vessels.[8,9] For this reason, in the present study we use a pulsatility ratio, which normalizes the velocity pulsatility in the MCA for systemic pressure pulsatility.[18] Finally, Grubb et al[6] did not measure systemic flow (cardiac output) or flow in other regional beds, nor did they evaluate lesser degrees of orthostatic stress. The absence of this information makes it difficult to draw conclusions from these data regarding the normal or abnormal blood pressure regulation during orthostasis.

The present study extends these previous observations by demonstrating the time course of changes in global cerebral blood flow velocity and pulsatility during graded reductions in central blood volume and cardiac filling in healthy subjects in the absence of drugs or reflex-mediated hypotension. Furthermore, we also provide a quantitative estimate of these changes in comparison to systemic and regional (forearm) flow and resistance as well as in comparison to hyperventilation, a maneuver known to markedly affect cerebral blood flow.

Like previous investigators,[26,28] we observed no change in cerebral blood flow velocity at lower levels of orthostatic stress in most subjects, despite the clear increase in systemic and forearm vascular resistances. However, as the level of LBNP increased, virtually all subjects had a decrease in MCA blood flow velocity and an increase in pulsatility ratio, presumably reflecting decreased blood flow and increased vascular resistance.

Traditionally, low levels of LBNP (< -20 mm Hg) are believed to cause primarily deactivation of cardiopulmonary receptors, resulting in increases in sympathetic nerve activity.[31] Because mean blood pressure and heart rate change little under such conditions, arterial baroreceptors have been considered to have little role until the level of LBNP increases to -40 mm Hg or greater.[32] In contrast, recent data from Mano et al[33] have shown a graded, linear relation between the degree of orthostatic stress during head-up tilt (sine of tilt angle) and sympathetic nerve activity. Moreover, the distinct fall in stroke volume and cardiac output that we observed in this and other studies[1,4] argues for some changes in the stimulus delivered to the baroreceptors,[34] even at low levels of LBNP. It thus is likely that either as a continuous function of decreasing cardiac filling pressures or discrete recruitment of arterial baroreceptors, a greater degree of sympathetic vasoconstrictor tone is required to constrict cerebral compared with peripheral arterioles.

This differential response between the cerebral and peripheral circulations may be due to a reduced sensitivity to sympathetic stimulation in the brain[35,36] and/or a compensatory autoregulatory response at the cerebral arteriolar level that overrides the sympathetic activation ("vasomotor escape").[37] Because mean blood pressure was well preserved until near-maximal LBNP, it is possible that autoregulatory mechanisms were not recruited, leaving sympathetic activity largely unopposed. It is more likely, however, that as we observed, autoregulation would maintain cerebral blood flow constant during low levels of orthostatic stress and moderate sympathetic activation. Ultimately, when the reduction in central blood volume is severe and the sympathetic nervous system is activated to a greater degree, the adrenergically mediated vasoconstriction may override autoregulatory metabolic vasodilatation and decrease cerebral blood flow. This model is consistent with the response in peripheral skeletal muscle during exercise, when maximal sympathetic activation may override local metabolic vasodilatory stimuli and cause vasoconstriction, even in active muscle.[38]

In a previous study,[4] we demonstrated that subjects who had increased ventricular compliance and thus large decreases in end-diastolic volume and stroke volume during LBNP (primarily endurance athletes) had low LBNP tolerance. In the present study, we observed that MCA blood flow velocity and presumably regional brain blood flow decreased coincident with systemic flow. Thus, the subjects with poor LBNP tolerance ("fainters") had a decrease in both cardiac output and MCA blood flow velocity at lower levels of LBNP than those who tolerated LBNP well. Subjects with good LBNP tolerance also had a decrease in cardiac output and MCA blood flow velocity but at greater levels of LBNP. We hypothesize, therefore, that in healthy individuals, sympathetic activation is greatest when the fall in cardiac volumes is greatest. As volume begins to fall rapidly (low levels of LBNP in fainters, higher in nonfainters), there is a baroreceptor-mediated increase in sympathetic activity, as evidenced by increases in forearm and systemic vascular resistances, which eventually leads to cerebral vasoconstriction.

Clinical Implications

Some patients with syncope or orthostatic hypotension may develop symptoms of dizziness without significant changes in cerebral perfusion pressure compared with asymptomatic patients.[39] These observations raise the question of whether the mild degree of cerebral vasoconstriction that we observed in the present study during central hypovolemia might lead to clinically significant alterations in cerebral autoregulation.

Possible Importance of the Sympathetic Nervous System in Cerebral Autoregulation

The role of the sympathetic nervous system in regulating cerebral blood flow has been a source of active controversy in the literature.[40,41] Cerebral blood vessels are richly innervated with adrenergic nerve fibers.[20] Under resting conditions, these nerves probably have little role in controlling cerebral blood flow,[42] at least in nonprimate species. However, under conditions of acute hypertension[43] or hypercapnia,[44] sympathetic activation clearly constricts cerebral blood vessels and probably is important in protecting the brain from severe hypertension.[45-48] This effect of sympathetic activity is likely greatest in large as opposed to small blood vessels.[49]

Moreover, there appears to be an important species difference in the response of cerebral blood flow to sympathetic stimulation.[50] Thus, in primates there is a prominent reduction in cerebral blood flow with sympathetic stimulation at rest[51] or even during hypotension,[52,53] as well as with hypertension as seen in other species. In summary, there appears to be adequate experimental evidence to suggest that sympathetic stimulation in primates, including humans, shifts both the

upper and lower limits of autoregulation to the right, minimizing the increase in cerebral blood flow at higher intravascular pressures.[20]

We speculate that during low levels of LBNP, the modest degree of sympathetic activation causes balanced large-vessel vasoconstriction and arteriolar vasodilatation (due to autoregulation) that maintain cerebral blood flow and velocity as measured in the MCA constant. With greater degrees of orthostatic stress, reduction in central blood volume and cardiac filling causes intense sympathetic activation, which results in mild arteriolar as well as large-vessel cerebral vasoconstriction. By itself, the reduction in cerebral blood flow velocity and presumably blood flow that we observed is not likely to compromise cerebral function or precipitate hemodynamic collapse. We believe this is true because hyperventilation, either alone or during LBNP, caused a more prominent reduction in blood flow velocity and increase in pulsatility than LBNP alone, yet never caused syncope. However, cerebral autoregulation is a dynamic process with substantial temporal heterogeneity.[54] Sympathetic activation may thus cause a dynamic shift in the autoregulatory range to the right (Fig 6), which, although protective during acute hypertension, may be detrimental during hypotension. Therefore, at the lower end of the pressure-flow relation (lower intravascular pressure), when arterial pressure finally does fall during LBNP, cerebral blood flow may be compromised at pressures that might otherwise be well tolerated, resulting in symptoms of presyncope. In the present study, all episodes of presyncope occurred suddenly, precipitated by a reduction in heart rate and blood pressure, which is consistent with the hypothesis that hemodynamic compromise is the primary initiating factor in such events.

Study Limitations

The primary limitation of this study is the fact that transcranial Doppler measures velocity rather than flow. The interpretation of changes in velocity depends on changes in vessel diameter both at the insonation site and in the downstream resistance vessels.[55] In the present study, we hypothesized that the observed reduction in velocity is due to a decrease in flow and an increase in downstream resistance. An alternative interpretation that would also be consistent with our observation of reduced velocity is that vasodilation occurred at the insonation site. However, proximal vasodilation would result in an increase in MCA blood flow, which is unlikely to occur during LBNP in the face of reduced cardiac output, and intense sympathetic neural activity, which if anything is likely to cause vasoconstriction rather than vasodilitation in the large conductance vessels of the cerebral circulation.[49] In fact, it is possible that some large-vessel vasoconstriction did occur during higher levels of LBNP due to sympathetic activation. If so, a reduction in diameter at the MCA would tend to increase velocity measured by transcranial Doppler and would cause us to underestimate the reduction in blood flow and/or degree of small-vessel vasoconstriction that is sufficient to result in a net decrease in velocity. The absence of any change in blood pressure during LBNP with added hyperventilation supports the hypothesis that at least this degree of vasoconstriction does not functionally impair cerebral metabolism, as long as blood pressure is maintained. We believe, therefore, that our interpretation of the Doppler changes is correct and that blood flow is likely to have decreased with an increase in downstream resistance.

Conclusions

We have demonstrated that cerebral blood flow velocity decreases during LBNP in healthy humans in the absence of systemic hypotension, probably as a result of sympathetic activation and vasoconstriction. The magnitude of this decrease is probably small, however, when compared with the prominent systemic and forearm vasoconstriction observed during LBNP or the cerebrovascular response to hyperventilation. Consequently, failure of cerebral autoregulation is not likely to be a primary cause of syncope during orthostatic stress in the absence of systemic hypotension. However, it may exacerbate the fall in cerebral blood flow associated with hypotension if hemodynamic instability develops.

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