The cerebral hemodynamics of normotensive hypovolemia during lower-body negative pressure

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Although severe hypovolemia can lead to hypotension and neurological decline, many patients with neurosurgical disorders experience a significant hypovolemia while autonomic compensatory mechanisms maintain a normal blood pressure. To assess the effects of normotensive hypovolemia upon cerebral hemodynamics, transcranial Doppler ultrasound monitoring of 13 healthy volunteers was performed during graded lower-body negative pressure of up to ~50 mm Hg, an accepted laboratory model for reproducing the physiological effects of hypovolemia. Middle cerebral artery flow velocity declined by 16% ± 4% (mean ± standard error of the mean) and the ratio between transcranial Doppler ultrasound pulsatility and systemic pulsatility rose 12% ± 8%, suggesting cerebral small-vessel vasoconstriction in response to the sympathetic activation unmasked by lower-body negative pressure. This vasoconstriction may interfere with the autoregulatory response to a sudden fall in blood pressure, and may explain the common observation of neurological deficit during hypovolemia even with a normal blood pressure.

Key Words: transcranial Doppler ultrasound • lower-body negative pressure • hypovolemia • sympathetic nervous system

INTRAVASCULAR volume depletion is an untoward state that commonly occurs in a variety of neurosurgical settings such as stroke, subarachnoid hemorrhage (SAH), and trauma, as well as during surgery on patients in the sitting position. Although this hypovolemia may progress to a frank fall in blood pressure, in most cases neurohumoral regulatory mechanisms can preserve blood pressure over significant periods of time. These homeostatic mechanisms include a powerful systemic vasoconstriction, and the consequent alterations in cerebral hemodynamics may be of clinical importance both during the normotensive phase of hypovolemia and during any subsequent neurological deterioration as blood pressure falls.

Prolonged stable periods of controlled normotensive hypovolemia are not common in the clinical setting, so there are few investigations of the associated hemodynamics. The laboratory technique of inducing lower-body negative pressure, however, has long provided a standard model for controlled hypovolemia. By applying a measured amount of negative pressure in a chamber sealed around a patient's lower extremities, graded central hypovolemia is easily produced and physiological variables can be readily monitored.

Physiological parameters change rapidly during lower-body negative pressure, so the method of cerebral hemodynamic monitoring must provide moment-to-moment information. Transcranial Doppler ultrasound has recently emerged as a tool permitting continuous monitoring and has been found useful in such disparate cases as assessment of cerebral vasospasm and guidance of carotid artery occlusion.

The purpose of this study is to document changes in cerebral hemodynamics during trials of lower-body negative pressure in man, using transcranial Doppler ultrasound technology, and to use these results as a model for the normotensive hypovolemia found in clinical practice.

Clinical Material and Methods

Thirteen healthy male volunteers (average age 27 ± 2 years) underwent graded lower-body negative pressure during continuous monitoring of transcranial Doppler ultrasound signals from the middle cerebral artery (MCA). All subjects had experienced several lower-body negative pressure trials previously. Seven of the subjects were trained athletes and had a measured oxygen uptake (VO2) maximum of 68 ± 7 ml/kg/min (mean ±
standard error of the mean). The remaining six were sedentary with a VO₂ maximum of 41 ± 4 ml/kg/min. The subjects were well matched for age, height, and weight and have been studied previously.  

Each subject was placed with the lower extremities in a pressure chamber which was sealed at the wrist; a graded vacuum was applied with a pump mechanism. The lower-body negative pressure protocol consisted of 40 minutes of baseline recording in the pressure chamber, followed by 15 minutes of negative pressure at −15 mm Hg, 5 minutes at −30 mm Hg, 15 minutes at −40 mm Hg, and finally 30 minutes at −55 mm Hg (Fig. 1). The study was discontinued in any patient who indicated symptoms or signs of presyncope, sudden onset of nausea, sweating, light headedness, bradycardia, hypotension, or a sustained decrease in systolic blood pressure below 90 mm Hg. This protocol has been used previously 16,17 and was approved by our Institutional Review Board. 

Blood pressure was monitored continuously with a finger plethysmography device, a device that has been previously well validated for arterial pressure monitoring during syncope induced by head-up tilt. 13 End-tidal CO₂ was monitored with a mass spectrometer† connected to a mouthpiece.

Doppler ultrasound signals were obtained from the MCA every 30 to 60 seconds during the protocol by means of a 2-mHz Doppler probe‡ attached to a headband and kept at a constant angle. Doppler signals consisted of a mean velocity and Gosling pulsatility, each averaged during four to five heartbeats. The velocity is proportional to flow if vessel diameter does not change, but increases if the insodated vessel vasoconstricts. 1,34

The Gosling pulsatility of a signal (defined as systolic velocity − diastolic velocity + by mean velocity) has been used as an index of hemodynamic resistance. 34 The pulsatility tends to increase as distal resistance rises as, for example, during the pial vasoconstriction of hyperventilation. However, the systemic blood pressure pulsatility delivered by the heart may dramatically change in conditions of lower-body negative pressure, and the Doppler ultrasound pulsatility will be directly affected. Accordingly, we have used the ratio between transcranial Doppler ultrasound and blood pressure pulsalities as a measure of the distal hemodynamic resistance.

The final 3 to 5 minutes of each level of lower-body negative pressure were considered to be most representative of steady-state conditions. The MCA flow velocities, pulsatility ratios, and blood pressures averaged over these time intervals were used for comparisons. Differences from baseline expressed as percentage changes were calculated for these quantities at each lower-body negative pressure level, and averages were obtained for the entire group, for the athletes, nonathletes, symptomatic subjects, and asymptomatic subjects. The groups were compared statistically with the t-test.

Results

Seven subjects developed symptoms of light-headedness or hypotension which ended the study, and six completed the entire protocol. Mean arterial blood pressure rose 6% ± 4% and pulse rate rose 40% ± 7% between the baseline and final values. The mean blood pressure fell 29% ± 9% during presyncope in subjects for whom measurements were available and precipitously in all seven subjects experiencing presyncope. The MCA flow velocities decreased by 16% ± 4% between baseline and final values (Fig. 2). These changes were significantly different from zero (p < 0.001), but there were no significant differences between the athletes and nonathletes or between the symptomatic and asymptomatic subjects.

Eight subjects achieved a lower-body negative pressure level of −50 mm Hg, four achieved a level of −40 mm Hg, and one achieved a level of −30 mm Hg. Values for physiological variables were calculated from baseline and final values in all subjects.

Pulsatility Ratio

There was a 22% ± 8% rise in pulsatility ratio between the baseline and final values (Fig. 3). This was significantly different from zero, but there were no significant differences between the athletes and nonathletes or between the symptomatic and asymptomatic subjects.

The rise in pulsatility ratios was considered early if there was at least a 20% increase at −15 or −30 mm Hg of lower-body negative pressure. Every subject with an early rise in this ratio became symptomatic and the only nonathlete with symptoms was the only nonathlete with an early pulsatility rise. Four subjects who displayed a sudden drop in blood pressure in the last few seconds of the protocol became symptomatic. The mean decrease in blood pressure at this time was 29% ± 9%.

Discussion

Physiological Changes During Lower-Body Negative Pressure

Cerebral blood flow (CBF) studies during lower-body negative pressure have been infrequent. 6,22,27,28,33 Nagasaka, et al. 22 reported a CBF decrease in rabbits using thermal probe methods, but quantitation of these changes was complicated by the nonlinear response of the probe. A comprehensive review by Wolthuis, et al. 33 describes a decrease in cerebral blood volume during lower-body negative pressure in animals. Davis and Sundt 1 showed a 24% decrease in CBF during

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![Graph showing lower-body negative pressure (LBNP) protocol.](image)

**Fig. 1.** Schematic representation of lower-body negative pressure (LBNP) protocol.

Nortmotensive hypovolemia induced by hemorrhage in cats, but considered that this response could not be proven to arise from sympathetic activation. Pearce and D’Alessy-Trabecan found a 17% fall in CBF after hemorrhage in anesthetized dogs accompanied by an increased cerebrovascular resistance. This response vanished during alpha receptor blockade by phenoxybenzamine. Sharma, et al., found a 25% decrease to -40 mm Hg in mean MCA flow velocities during lower-body negative pressure in seated humans and noted a depressed diastolic velocity in the group experiencing syncope. Although human CBF data are scant, it seems likely that there is a moderate fall in CBF during normotensive hypovolemia.

On the other hand, the systemic events occurring during lower-body negative pressure have been extensively studied. The application of a negative pressure of -50 mm Hg is followed by venous pooling in the lower extremities of 500 to 1000 cc, and by a fall in central venous pressure of 3 to 7 mm Hg. Deactivation of baroreceptors results in removal of tonic sympathetic inhibition and an increase in sympathetic efferent activity, leading to a strong increase in peripheral vasoconstriction and a decrease in skeletal muscle blood flow. It is of interest to our study that the systemic pulse pressure falls even when mean pressure remains constant, so there is a decrease in systemic pulsatility. A mechanism for the commonly observed hemodynamic collapse and subsequent syncope has been proposed by Epstein, et al., in which a marked decrease in systolic and diastolic ventricular volumes activates cardiac vagal afferents which trigger a central depressor reflex and bradycardia.

**Interpretation of Doppler Ultrasound Findings**

The cerebral changes detected by transcranial Doppler ultrasound monitoring during these events were a 16% drop in MCA flow velocity accompanied by a 22% rise in the pulsatility ratio. This suggests a drop in CBF and an increase in cerebral resistance due to small-vessel cerebral vasoconstriction of a magnitude comparable to that found in previous studies. Furthermore, an autonomic pial or arteriolar vasoconstriction might impede any autoregulatory dilatory response to a fall in

![Graph showing MCA velocity, mean systemic blood pressure, and the pulsatility ratio.](image)

**Fig. 3.** Graphs of data from one subject showing mean middle cerebral artery (MCA) velocity, mean systemic blood pressure, and the pulsatility ratio. Lower-body negative pressure of -15 mm Hg was started at 11 minutes, -30 mm Hg at 27 minutes, and -40 mm Hg at 32 minutes. The patient became symptomatic at 36 minutes.

![Tracings of transcranial Doppler ultrasound velocity waveforms.](image)

**Fig. 2.** Tracings of transcranial Doppler ultrasound velocity waveforms taken from the middle cerebral artery in normal state (upper left), at the end of lower-body negative pressure (upper right), and during moderate hyperventilation (lower).
blood pressure and shift the cerebral autoregulation curve to the right. In fact, this shift has been described during sympathetic stimulation, and a shift in the opposite direction has been found during sympathetic blockade and chemical sympathectomy.

A small-vessel vasconstriction with an impairment of autoregulation also explains the extreme sensitivity of neurological signs upon blood pressure and pulse at the end of the lower-body negative pressure trials. The 29% fall in blood pressure occurring before syncope might ordinarily be well tolerated by young, healthy subjects, and we speculate that the CBF is abnormally dependent upon blood pressure and pulse when impaired by the demonstrated small-vessel vasconstriction. A moderate fall in blood pressure and relative bradycardia would then rapidly lead to cerebral ischemia and syncope. Only in the setting of a more marked and gradual decrease in mean arterial blood pressure would autoregulatory mechanisms efficiently compensate for this cerebral vasconstriction. Furthermore, these presyncopeal changes are unlikely to be a result of the small-vessel vasconstriction alone, since an intense vasconstriction with similar transcranial Doppler ultrasound waveforms is seen without syncope in voluntary hyperventilation (Fig. 2).

In this study, the inference of small-vessel cerebral vasconstriction is based on the rise in pulsatility ratio, and a minor role is assumed for diameter changes in the larger vessels which are actually insonated. It is therefore useful to consider what the effects might be of any such changes in diameter. In general, vasconstriction at the insonation site will lead to an increased velocity and a decreased pulsatility, whereas distal small-vessel vasconstriction will yield a decreased velocity and increased pulsatility. Furthermore, the constancy of vessel diameter cannot be assumed during the sympathetic stimulation of lower-body negative pressure, especially since the large cerebral vessels are known to be richly innervated with autonomic fibers. Although an MCA dilation would explain the observed decrease in velocity and increase in pulsatility ratio, a constriction is more likely since resistance in the large vessels is known to rise during hemorrhage and since a decrease in vessel diameter during hemorrhage has been directly observed in angiographic studies.

An MCA vasconstriction would lead to a velocity increase and pulsatility decrease, so one must infer a small-vessel vasconstriction in order to explain the opposite changes we observed during lower-body negative pressure. This is contrary to other theories, which propose a sympathetic proximal constriction and an autoregulatory distal vasodilation, which arises during hypovolemia accompanied by hypotension and is presumably metabolically mediated following the resulting ischemia. Our protocol of hypovolemic normotension, however, does not induce ischemia, so only triggers a sympathetic vasconstriction without any offsetting metabolic vasodilating stimulus. Similar vasocconstrictive decreases in CBF have been noted following sympathetic stimulation and the fact that we did not observe a slow "escape" to normal values may have been due either to the progressively severe hypovolemic challenge of our lower-body negative pressure protocol or to the lack of hypotension and vasodilatory stimulus.

It should also be noted that our observed velocity decrease of 16% is close to estimates of the CBF decrease during lower-body negative pressure and during sympathetic stimulation, suggesting that the magnitude of MCA diameter change is small. Furthermore, angiographic studies have noted a 7% or smaller change in MCA diameter under the intense sympathetic stimulation of hemorrhagic hypotension, supported by diameter calculations derived from measurements of resistance changes. It seems reasonable, therefore, to conclude that in lower-body negative pressure there is a small-vessel vasconstriction leading to a moderate decrease in CBF, a relative increase in pulsatility, and an impairment in autoregulation.

Validity of Model

Although pulsatility indices derived from transcranial Doppler ultrasound waveforms are commonly used as indices of cerebrovascular resistance, the systemic pulsatility also decreased significantly during our lower-body negative pressure protocol, as has been described elsewhere. We therefore used a ratio of cerebral to systemic pulsatility to compensate for this change. However, since a significant portion of cardiac output is directed to the brain, any cerebral vasconstriction may itself increase the systemic pulsatility, and the ratio may in fact underestimate the degree of cerebral vasconstriction.

The hematocrit is relatively constant during lower-body negative pressure, so dilution cannot be implicated as a cause of the observed velocity increase. Furthermore, the decrease in central and wedge pressures known to occur during lower-body negative pressure and observed in our population in an earlier study is mild and not likely to influence intracranial pressure or cerebral perfusion pressure or to overwhelm autoregulatory compensation to lead to an increase in MCA velocity.

Clinical Relevance

The presence of significant volume depletion with a normal blood pressure occurs in several clinical settings of interest to the neurosurgeon. Patients who have suffered SAH after aneurysmal rupture are commonly hypovolemic, and the efficacy of volume repletion independent of changes in blood pressure is well documented. A similar situation can exist for the patient with an acute cerebral infarct, and volume depletion is common in the patient with multiple traumatic injuries. Patients placed in the sitting position during neurosurgical procedures can also experience normotensive hypovolemia. Despite the potential neurological signifi-
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cance of this pathological state, the exact effects of normotensive hypovolemia on human cerebral hemodynamics have not been extensively studied. Instead, many reports focus on later stages of hypovolemia in which blood pressure has fallen and evoked ordinary cerebral autoregulatory mechanisms. In this report, we have studied 13 subjects during graded lower-body negative pressure with transcranial Doppler ultrasound as a model for normotensive hypovolemia.

These observations have clinical significance for the patient with vasospasm. The added cerebrovascular resistance induced by hypovolemia lowers the "critical" level of stenosis at which hemodynamic compromise occurs and can potentially lead to earlier neurological decline as the vasospasm increases. The associated impairment in autoregulation may further add to the autoregulatory dysfunction known to occur in SAH. Finally, reversal of the hypovolemia and its attendant vasocostriction would explain why some patients improve with volume repletion even when blood pressure itself is not altered.

In this study, we used lower-body negative pressure as a model of the normotensive hypovolemia occurring in a number of clinical situations. of interest to the neurosurgeon. The transcranial Doppler ultrasound data suggest that cerebral vasoconstriction occurs in the periphery in response to the sympathetic stimulation of hypovolemia. This suggests a mechanism of enforced hyperperfusion until autoregulatory mechanisms are triggered by a frank decrease in cerebral perfusion pressure and explains why even moderate hypovolemia can be detrimental to the neurologically impaired patient.

Acknowledgments

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