

Cerebral Hemodynamics During the Valsalva Maneuver

Insights From Ganglionic Blockade

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Background and Purpose—The aim of this study was to differentiate the mechanical effects of the Valsalva maneuver (VM) from the effects of changes in autonomic neural activity on cerebral hemodynamics in humans.

Methods—Nine healthy subjects performed the VM before and after autonomic ganglionic blockade with trimethaphan. Blood pressure (BP) was measured in the radial artery with an indwelling catheter or at the finger by Finapres. Cerebral blood flow (CBF) velocity was measured in the middle cerebral artery with transcranial Doppler; end-tidal CO₂ was measured by mass spectrometry.

Results—Before blockade, during phase II of the VM, BP was reduced by 27% and CBF velocity was reduced by 33% (magnitude of changes during phase II divided by baseline measurements before the VM, $P < 0.05$). Cerebrovascular conductance index (CVCI) increased by 21%. During phase IV, overshoot of CBF velocity was proportionately greater than that of BP (46% versus 30%). After blockade, during phase II, BP fell to a much greater degree by 50%, while CBF velocity decreased even more by 60% associated with an increase in CVCI by 33%. During phase IV, despite the absence of BP overshoot, CBF velocity still increased by 55% and CVCI by 33%. Both were significantly greater than before blockade.

Conclusions—After ganglionic blockade, cerebral autoregulation is unable to prevent the substantial fall in CBF induced by the marked reduction in BP during the VM. Enhanced phase IV increases in both CBF velocity and CVCI reflect the intrinsic characteristics of cerebral hyperemic responses, which are likely modified in part by the removal of vasoconstrictor effects of autonomic neural activity elicited during the VM. (*Stroke*. 2004;35:843-847.)

Key Words: blood pressure ■ cerebral blood flow ■ ultrasonography, Doppler

Intrathoracic pressure changes with respiration, which exerts mechanical effects on and evokes autonomic reflexes in the systemic and cerebral circulations.^{1,2} One circumstance that has been studied extensively is the Valsalva maneuver (VM), defined as a forced expiratory blow against a closed glottis.^{1,3} Valsalva maneuvers are performed both voluntarily and involuntarily during daily life under many conditions such as coughing, defecation, and heavy weightlifting.^{1,4} Associated with different levels of expiratory strain, intrathoracic pressure may increase from only a few to >150 mm Hg in healthy subjects.¹ Such large increases in intrathoracic pressure alter the systemic and cerebral circulations dramatically and could precipitate cerebral catastrophes.^{5,6}

Under experimental conditions, phasic changes in blood pressure (BP) and other cardiovascular variables during the VM have been well characterized to examine the integrity of autonomic function.^{2,7} However, owing to the relative inaccessibility of the cerebral circulation and the limitations in technology for the measurement of cerebral blood flow (CBF) with high temporal resolution, changes in cerebral hemodynamics during the VM have rarely been studied.

Recently, it has been shown with transcranial Doppler (TCD) that CBF velocity is reduced during early phase II and overshoots during phase IV of the VM.⁸⁻¹⁰ In addition, a ratio of changes in CBF velocity over BP during phase II or IV of the VM has been used to assess cerebral autoregulation in patients with carotid artery stenosis.⁸ These observations extended previous studies measuring CBF invasively during the VM.¹¹

However, because changes in cerebral hemodynamics during the VM are likely mediated by both the mechanical effects of changes in intrathoracic pressure and the elicited autonomic neural activity,^{1,2,7,12} the mechanical effects of the VM alone on the cerebral circulation are not known. This question is essential not only because it is physiologically interesting but also because of potentially significant clinical implications. For example, in patients with impaired autonomic function, the magnitude of BP reduction during a routine VM is substantially greater than in normal subjects.^{1,2} Occasionally, syncope or even death may occur under these circumstances.^{1,5,6} However, changes in cerebral hemodynamics under these conditions (ie, primarily the mechanical effects of the VM) have not been elucidated.

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The purpose of this study was to differentiate the mechanical effects of the VM from the effects of changes in autonomic neural activity on cerebral hemodynamics in humans. Autonomic neural activity elicited during the VM was removed by ganglionic blockade with trimethaphan. We hypothesized that the magnitude of the decrease in CBF velocity during phase II and the overshoot of CBF velocity during phase IV of the VM would be enhanced significantly by ganglionic blockade.

Subjects and Methods

Nine healthy subjects, 6 men and 3 women, with a mean age of 30 ± 6 years (range, 23 to 38 years), height of 171 ± 10 cm, and weight of 69 ± 11 kg participated in this study. All subjects signed an informed consent form approved by the Institutional Review boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

BP was measured with a radial arterial catheter ($n=3$) (Abbott Critical Care System) or by Finapres (Ohmeda). Because no significant difference was observed between the 2 methods, all data were pooled together for statistical analysis. CBF velocity was recorded from the middle cerebral artery (MCA) with TCD. A 2-MHz probe (Multiflow, DWL) was placed over the subject's temporal window and fixed at a constant angle with a probe holder to secure the probe position during the experiments. Heart rate was monitored by ECG, and end-tidal CO_2 (ETCO_2) was measured by a mass spectrometer (Marquette Electronics).

All experiments were performed in the morning at least 2 hours after a light breakfast. After at least 30 minutes of supine rest, 2 baseline VMs were performed with a 5-minute interval between the tests. In general, the first VM was considered practice, and the second was used for data analysis. Specifically, after 1 minute of spontaneous breathing on the mouthpiece, at the end of a normal inspiration, the subject was asked to blow out against an obstructed airway and to maintain expiratory pressure of 30 mm Hg for 15 seconds.^{2,7} The mouthpiece was connected to an analog manometer to monitor expiratory pressure carefully during the VM. After the baseline VMs, trimethaphan was infused intravenously (6 to 7 mg/min, trimethaphan camsylate, Cambridge Laboratories).¹³ The absence of heart rate response to changes in BP indicates the efficacy of ganglionic blockade (Figure 1).¹³ The VM was performed once again to assess the mechanical effects of the VM on the cerebral circulation.

Beat-to-beat BP and CBF velocity obtained for 15 seconds before the VM were averaged as baseline. ETCO_2 obtained from the first 2 breaths immediately after the release of expiratory strain was averaged to reflect the changes in arterial CO_2 during the VM.¹⁰ Phasic changes in BP and CBF velocity during the VM were defined as those reported previously (Figure 1).^{2,8,10,11} Of note, after blockade, because BP and CBF velocity were reduced continuously during phase II and no clear peaks could be identified easily during phase IV of the VM (Figures 1 and 2), the phase IIa and IV values of BP and CBF velocity, respectively, were obtained at the same time points as those measured before blockade. In addition, relative changes in BP and CBF velocity during the VM were calculated as the ratio of the magnitude of the phasic changes during the VM divided by the baseline measurements before the VM.

Finally, to assess changes in cerebrovascular conductance, a cerebrovascular conductance index (CVCI) was calculated as mean CBF velocity divided by mean BP under resting conditions and during phase IV of the VM, assuming that intracranial pressure (ICP) and cerebral venous pressure are low and remain relatively constant under these conditions (ie, with no straining).^{10,11} During expiratory strain, CVCI was calculated as mean CBF velocity divided by the estimated cerebral perfusion pressure (CPP), calculated as changes in mean BP minus the expiratory pressure, which approximates changes in intrathoracic and thus cerebral venous pressure and ICP.^{1-3,10} Of note, owing to the difficulty in estimating transient

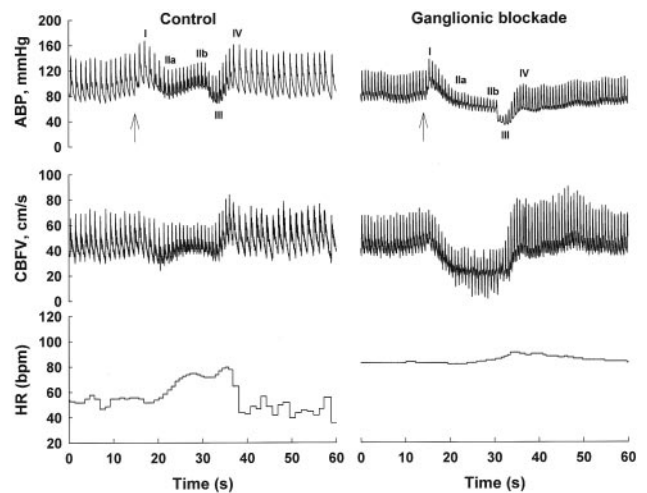


Figure 1. Representative recordings of arterial pressure (ABP, arterial line), CBF velocity (CBFV), and heart rate (HR) during the VM before and after ganglionic blockade. Note that the slight increase in heart rate during phases III and IV was likely induced by mechanical stretching of the sinus node associated with cardiac refilling after release of expiratory straining. Vertical arrows indicate onset of the VM.

changes in CPP during the rapid phase I and phase III of the VM, CVCI was not calculated under these conditions.

Data obtained before and after blockade were compared by 2-way repeated-measures analysis of variance with the VM and ganglionic blockade as the main experimental factors. When significant differences were detected, Student-Newman tests were used for post hoc comparisons. Comparisons of ETCO_2 between baseline and after release of expiratory strain were performed by paired *t* tests. Data are presented as mean \pm SE. The significance level was set at $P < 0.05$.

Results

VM Before Blockade

Representative changes in BP, CBF velocity, and heart rate are shown in Figure 1. Group-averaged results are shown in Figure 2. During phase I, BP increased, whereas CBF velocity did not change (Figures 1 and 2 and Table 1). During

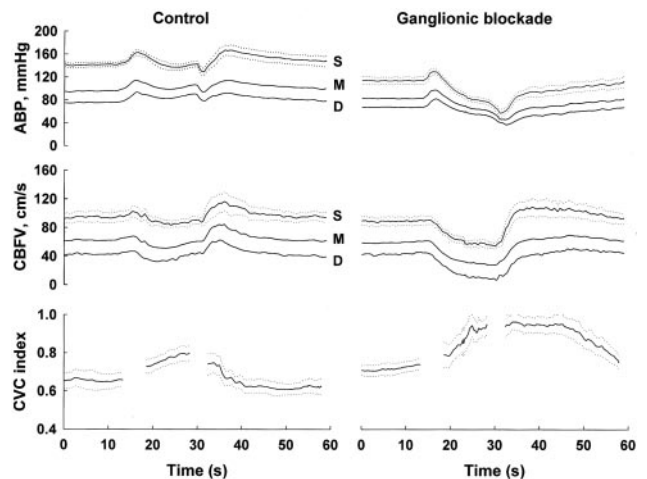


Figure 2. Group-averaged systolic (S), mean (M), and diastolic (D) arterial pressure (ABP); CBF velocity (CBFV); and calculated CVCI during the VM before and after ganglionic blockade ($n=9$). Solid lines show means; dotted lines, mean \pm SE.

TABLE 1. Phasic Changes in Arterial Pressure and CBF Velocity During the VM

	Control						Ganglionic Blockade					
	Rest	I	Ila	Ilb	III	IV	Rest	I	Ila	Ilb	III	IV
SBP, mm Hg	142±4	169±5*	134±5	145±5	123±6*	169±9*	115±6‡	135±5‡	91±4‡	75±4‡	49±4‡	94±8‡
MBP, mm Hg	96±2	120±4*	95±4	109±4*	85±8*	113±4*	83±5‡	102±4‡	71±2‡	60±3‡	41±3‡	67±7‡
DBP, mm Hg	76±2	100±3*	79±5	93±5*	74±5	93±4*	68±4‡	85±3‡	60±2‡	53±3‡	36±2‡	53±5‡
CBFV _s , cm/s	95±7	102±7	83±5	91±6	87±5	122±13*	89±6	92±6‡	65±4‡	58±5‡	56±4‡	108±11‡
CBFV _M , cm/s	63±4	70±4	48±3*	62±4	59±4	89±10*	60±3	63±4	35±2‡	28±3‡	31±3‡	65±8‡
CBFV _D , cm/s	43±3	50±3	30±4*	44±4	43±4	66±8*	43±2	47±3	18±3‡	7±3‡	15±3‡	44±7‡
CVCI, cm · s ⁻¹ · mm Hg ⁻¹	0.66±0.04		0.78±0.04*	0.74±0.05		0.73±0.05	0.72±0.03		0.84±0.06‡	0.96±0.05‡		0.95±0.04‡

SBP indicates systolic pressure; MBP, mean blood pressure; DBP, diastolic pressure; CBFV_s, systolic CBF velocity; CBFV_M, mean CBF velocity; and CBFV_D, diastolic CBF velocity. Values are mean±SE; n=9.

*P<0.05, comparisons between the rest and changes during the VM before blockade.

‡P<0.05, comparisons between the rest and changes after blockade.

‡P<0.05, comparisons under the same conditions before and after blockade.

phase IIa, mean and diastolic CBF velocities were reduced by 33% and 44%, respectively, despite a significant increase in CVCI by 21% (Figure 2 and Tables 1 and 2). During phase IIb, mean and diastolic pressures increased above the baseline level, and CBF velocity returned to the baseline before the VM. During phase III, BP was reduced, whereas CBF velocity did not change (Figures 1 and 2 and Table 1). During phase IV, overshoots of systolic, mean, and diastolic CBF velocities all were greater than those in BP (Figures 1 and 2 and Tables 1 and 2). Of note, these overshoots returned quickly to baseline levels in ≈10 seconds, associated with a reduction in CVCI (Figures 1 and 2 and Table 1). ETCO₂ did not change significantly during the VM (before, 36±1 mm Hg; after, 38±2 mm Hg; P=0.08).

VM After Blockade

After blockade, BP under resting conditions was reduced, associated with a slight reduction in CBF velocity (Figures 1 and 2 and Table 1). During phase I, similar to before blockade, BP increased whereas CBF velocity did not change (Figures 1 and 2 and Table 1). However, it is striking to see that during phase II, despite an increase in CVCI by >33%, mean CBF velocity was reduced substantially by 60% in response to the greater fall in BP by 50% (Figures 1 and 2 and Tables 1 and 2). Of note, in 5 of the 9 subjects, diastolic CBF

velocity was reduced to 0 with an average group reduction by 93% (Figures 1 and 2 and Tables 1 and 2). During phase III, BP was reduced further, whereas no further reduction in CBF velocity was observed (Figures 1 and 2 and Tables 1 and 2). In addition, regardless of the presence or absence of blockade, no difference in the magnitude of BP changes was observed between phases I and III of the VM (Table 2).

Finally, during phase IV, despite the absence of BP overshoot, CBF velocity increased rapidly and was maintained at a high level ≈20 seconds before BP returned to baseline (Figures 1 and 2 and Table 1). Consequently, CVCI increased significantly by 33% and remained elevated during phase IV of the VM (Figure 2 and Table 1). Importantly, the magnitude of the phase IV increases in both CBF velocity and CVCI was significantly greater than before blockade (Figures 1 and 2 and Tables 1 and 2).

Discussion

There are 2 primary new findings in this study. First, with ganglionic blockade, CBF velocity during phase II of the VM was reduced substantially after a marked reduction in BP. Second, despite the absence of BP overshoot, the magnitude of phase IV increases in CBF velocity was enhanced significantly compared with that before ganglionic blockade. In the following discussion, we focus on the methodological limi-

TABLE 2. Relative Changes in Arterial Pressure and CBF Velocity During the VM

	Control, %				Ganglionic Blockade, %			
	I–Rest	I–IIa	IIb–III	IV–III	I–Rest	I–IIb	IIb–III	IV–III
SBP	19±2	25±4	16±2	32±6	18±2	53±3*	23±1	38±5
MBP	26±2	27±3	26±6	30±8	23±3	50±3*	24±2	30±6
DBP	32±2	27±4	26±3	26±7	27±3	49±3*	25±2	24±6
CBFV _s	8±2	19±3	4±2	34±7	3±1	37±4*	2±4	56±7*
CBFV _M	12±3	33±4	5±2	46±8	6±2	60±3*	-5±2	55±10*
CBFV _D	17±4	44±8	6±6	53±12	8±2	93±7*	-18±7	65±11*

Abbreviations as in Table 1. Values are mean±SE; n=9. Note that because both arterial pressure and CBF velocity after blockade were reduced continuously during phase II, the relative changes were calculated as (I–IIb)/rest after blockade instead of (I–IIa)/rest before blockade.

*P<0.05, comparisons between before and after blockade.

tations, possible mechanisms responsible for these observations, and potential clinical implications of this study.

Regulation of CBF During the VM: Before Blockade

The underlying mechanisms for CBF control during the VM are unknown. In the present study, before blockade, CVCI increased significantly during early phase II of the VM, associated with reductions in CBF velocity. These data, consistent with previous studies,^{8,11} suggest the presence of cerebral myogenic autoregulatory responses to transient reductions in CPP.¹¹

During late phase II, elevated ICP likely remained constant owing to the stable intrathoracic pressure.^{3,11} Hence, CPP and therefore CBF velocity increased after an increase in BP. Of note, CVCI during late phase II, if anything, was slightly reduced compared with early phase II (Table 1). These data suggest the presence of cerebral vasoconstrictor responses to the increases in CPP. However, sympathetic activation elicited during the VM also may play a role in this process.^{7,12,13}

During phase IV, the overshoot of CBF velocity was proportionately greater than BP. This difference may reflect a delayed cerebral vasodilation evoked during early phase II of the VM⁸ or conversely could be mediated by a reduction in cerebral critical closing pressure during phase IV of the VM.⁹ It should be emphasized that during phase IV of the VM, elevated CVCI returned rapidly to the baseline level associated with the recovery of BP and CBF velocity (Figure 2). Two regulatory mechanisms may be responsible for this process. First, a rapid washout of brain metabolites (accumulated during the VM) via the overshoot of CBF may lead to the reduction in CVCI. Second, the overshoot of arterial pressure and/or sympathetic activation elicited during the VM may cause cerebral vasoconstriction myogenically and/or neurally and lead to the reduction in CVCI.^{7,12,13}

Regulation of CBF During the VM: After Blockade

Cerebral autoregulatory responses during the VM could be confounded by the presence of potent sympathetic activation during the VM elicited by the baroreflex⁷ and/or an increase in ICP.¹⁴ In the present study, with autonomic blockade, we observed that during phase II of the VM, CBF velocity decreased continuously and substantially after a marked fall in BP. Of note, CVCI further increased during late phase II while the reductions in BP and CBF velocity persisted. These data demonstrate convincingly the presence of cerebral autoregulatory responses to the greater fall in BP. However, these data also demonstrate clearly the inability of autoregulation to maintain a relatively constant CBF under dynamic conditions.¹¹

Interestingly, during phase IV of the VM, despite the absence of BP overshoot, the magnitude of increases in both CBF velocity and CVCI was enhanced substantially compared with before blockade. Moreover, increases in both CBF velocity and CVCI were sustained and prolonged over a time period of about 20 seconds before BP slowly returned to the baseline level (Figure 2). These observations are remarkably similar to the time course characteristics of cerebral reactive

hyperemia observed in animals¹⁵ and therefore strongly suggest the presence of cerebral hyperemic responses evoked by the VM after ganglionic blockade.

Two mechanisms may be responsible for these changes. First, the enhanced increase in both CBF velocity and CVCI may be mediated simply by a greater metabolic and/or myogenic stimulation of the cerebral circulation that is associated with the severe hypotension and/or cerebral ischemia that occurred during the VM. Second, removal of vasoconstrictor effects of sympathetic activation elicited during the VM by ganglionic blockade also may enhance the magnitude of increases in CBF and CVCI during phase IV of the VM.^{7,12,13}

Finally, regardless of the presence or absence of blockade, we found no difference in the magnitudes of BP changes between phases I and III. These observations provide further evidence that changes in BP during phases I and III of the VM are mediated primarily by the mechanical effects of changes in intrathoracic pressure.^{1,2} Moreover, the findings that CBF velocity did not change during these phases are consistent with the observations that ICP and cerebral venous pressure change in parallel with changes in arterial pressure; thus, CPP and CBF would remain constant under these conditions.^{3,10}

Clinical Implications

After blockade, mean and diastolic CBF velocities decreased dramatically by 60% and 93% during phase II of the VM. These data may provide useful insights into the underlying mechanisms responsible for the incidence of syncope in autonomic failure patients and in patients with abnormalities of BP regulation.⁵ Conceivably, if BP regulation is impaired and reduced dramatically during a VM or posture change in daily life, substantial reductions in CBF are likely to occur. A large, sustained reduction in CBF may ultimately lead to syncope.⁵ Moreover, after blockade, the time course of the increase in CBF velocity during phase IV of the VM likely reflects the characteristics of cerebral hyperemic responses in humans.¹⁵ Therefore, using the model provided in this study to identify the control mechanisms of cerebral hyperemic responses may have potential implications for patient care under many clinical conditions of brain injury.

Study Limitations

First, to assess changes in CPP, we would have to measure BP simultaneously with ICP and/or cerebral venous pressure.^{10,11} Earlier studies in humans have demonstrated clearly that during the VM, cerebrospinal fluid pressure increases immediately and in parallel to the rise in intrathoracic pressure.³ Recent studies also showed that cerebrospinal fluid pressure and ICP increased during the VM in patients after neurosurgical operations.^{4,11} In addition, central venous pressure and internal jugular venous pressure increased to the same extent as intrathoracic pressure, which approximates the expiratory pressure during the VM.^{1-3,10} Of note, the magnitude of changes in intrathoracic pressure during the VM did not change after autonomic blockade.² Thus, in the present study, CPP during the VM was estimated from mean BP minus the expiratory pressure.

Second, we measured CBF velocity in the MCA to reflect changes in CBF. Changes in CBF velocity reflect changes in CBF only if the diameter of the insonated MCA remains constant. Recently, several studies have used TCD to measure CBF velocity during the VM.^{8–10} Data showed that phasic changes and the magnitude of changes in CBF velocity are consistent with the changes in CBF measured invasively with electromagnetic flowmetry in the internal carotid artery.¹¹ These observations argue for the validity of using TCD in this study. However, we cannot exclude the possibility that a vasodilation in the MCA may occur after ganglionic blockade. Thus, changes in CBF may be underestimated by the measurement of CBF velocity. However, if this is the case, our conclusion of greater reductions in CBF during phase II and greater increases in CBF during phase IV of the VM should be strengthened rather than weakened under these circumstances.

In summary, we have demonstrated prominent mechanical effects of the VM on the cerebral circulation in humans. We found that after autonomic blockade, despite the presence of cerebral autoregulatory responses, CBF velocity was reduced substantially after a marked fall in arterial pressure during phase II of the VM. Moreover, the magnitude of phase IV increases in both CBF velocity and CVCi was enhanced significantly and demonstrates the intrinsic characteristics of cerebral hyperemic responses in humans. These data emphasize the dynamic pressure-flow relationship of the cerebral circulation and provide new insights into the regulation of CBF during the VM.

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