[Clinical Studies]

Effect of Transient Moderate Hyperventilation on Dynamic Cerebral Autoregulation after Severe Head Injury

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Abstract

OBJECTIVE: This study was undertaken to evaluate the effect of acute moderate hyperventilation on cerebral autoregulation in head-injured patients.

METHODS: Dynamic cerebral autoregulation was analyzed by use of transcranial doppler ultrasonography before and after hyperventilation in 10 patients with severe head injury. All of the patients were artificially ventilated and underwent continuous monitoring of arterial blood pressure, intracranial pressure, and end-tidal carbon dioxide. To test autoregulation, rapid transient decreases in systemic blood pressure were achieved by quickly releasing large blood pressure cuffs that were inflated around both thighs. This resulted in a drop of 24 ± 6 mm Hg in mean systemic blood pressure, which lasted an average of 49 ± 24 seconds. Cerebral blood flow velocity was monitored continuously in both middle cerebral arteries by use of transcranial doppler ultrasonography. The percentage change in middle cerebral artery velocity was used as an index of the change in cerebral blood flow during the autoregulatory response. The change in estimated cerebrovascular resistance, immediately after the blood pressure drop, or the rate of regulation was used to analyze the effectiveness of the cerebral autoregulation. This value was calculated by determining the rate of increase in middle cerebral artery velocity during the 1st 5 seconds after a blood pressure drop, relative to the rate of increase of the cerebral perfusion pressure.

RESULTS: The average rate of regulation during normocapnia at pCO_2 of 37 mm Hg was $11.4 \pm 5\%$ per second. After reduction of the pCO_2 to 28 mm Hg, the average rate of regulation improved significantly ($P < 0.001$) to $17.7 \pm 6\%$ per second. Autoregulation improved, despite no significant change in the cerebral perfusion pressure during hyperventilation. The degree of improvement in autoregulation was significantly correlated with the CO_2 reactivity (r = 0.45, $P < 0.05$) but did not correlate (r = -0.23, $P = 0.33$) with the change in arterial pH value after hyperventilation.

CONCLUSION: These results confirm the finding that dynamic autoregulation is disturbed in severe head injury and that moderate transient hyperventilation can temporarily improve the efficiency of the autoregulatory response, probably as a result of a transient increase in vascular tone.

Cerebral autoregulation refers to the ability of the brain to maintain relatively constant blood flow under conditions of changing cerebral perfusion pressure (CPP) (40). Under normal circumstances, changes in blood pressure induce rapid dynamic changes in distal cerebral resistance vessels that constrict or dilate to maintain the cerebral blood flow (CBF) at near constant levels, within a defined range of CPP (40). Severe head injury disrupts the autoregulatory mechanism to some degree in most patients (9, 17-19, 33, 38). Impaired autoregulation after head injury may contribute to secondary brain injury by several mechanisms (27). For example, increased intracranial pressure (ICP) and/or episodes of hypotension may cause a reduced CPP. In turn, reductions in the CPP may result in critical reductions in the CBF and cause cerebral ischemia when autoregulation is absent (17, 38). Moreover, sudden increases in the CPP may be more likely to cause secondary edema and delayed hemorrhage if autoregulation is absent (26, 44). ICP A waves, or plateau waves, may in part be mediated by an increase in the latency of the autoregulatory response, and A waves may also cause delayed deterioration in head-injured patients (37, 43). Many of the current treatments used in head-injured patients exert their actions partially through their effects on the cerebral vasculature and, therefore, require autoregulation to be present for maximal effect (29, 30, 34). Thus, it is important to understand the nature of impaired autoregulation. In patients with impaired autoregulation, Paulson et al. (39) demonstrated that moderate hyperventilation resulted in improvement in the autoregulatory response. Moreover, in healthy volunteers, autoregulation can be impaired by hypoventilation and can be improved by moderate hyperventilation (4). The improvement in autoregulation in these studies, however, was accompanied by an overall decrease in the CBF. In the present study, we tested the hypothesis that impaired autoregulation after human head injury can be improved transiently by transient moderate hyperventilation.

Most studies that demonstrated impaired cerebral autoregulation after head injury in humans used static measurements of the CBF at equilibrium and then repeated measurements after an induced step change in systemic blood pressure by use of vasoactive medications (9, 12, 33, 38). Evaluation of the dynamic cerebral autoregulatory response by use of transcranial doppler ultrasonography (TCD) has been previously described (4), and its validity has been confirmed (6, 36, 46). This technique uses the continuous measurement of blood flow velocity from the middle cerebral artery(MCA), during transient decreases in blood pressure. The relative changes in MCA velocities (MCAVs) during this decrease are an index of relative blood flow change during the autoregulatory response. Impairments in dynamic cerebral autoregulation have recently been strongly correlated with impaired autoregulation measured by means of more prolonged or static blood pressure changes (46). In the present study, we used TCD, arterial blood pressure (ABP), and ICP recordings to test dynamic autoregulation before and after moderate hyperventilation.

PATIENTS AND METHODS

Patients with severe head trauma (Glasgow Coma Scores of <=8 at initial evaluation) who had been admitted to Harborview Medical Center in Seattle, Washington, were studied. The reasons for exclusion from the study included hemodynamic instability, pulmonary compromise, and severe lower extremity trauma. Computed tomographic scans were obtained for all of the patients at the time of admission and repeated within 24 hours of injury. After full evaluation and treatment of acute injuries, patients were admitted to the intensive care unit, in which they were mechanically ventilated and had continuous monitoring of the radial ABP, ICP, and end-tidal carbon dioxide (ET CO_2). Sedatives, analgesics, and paralytics were routinely administered as needed. The testing described was performed within 24 hours of injury in all of the patients. The study was approved by the Human Subjects Committee of the University of Washington. Written, informed consent was obtained from family members of the patients before each study.

The demographic characteristics of the subjects entered into the study are shown in Table 1. The mean age was 35.6 years (range, 17-74 yr). The mechanisms of injury were motor vehicle accidents for three patients, bicycle accidents for two, assault for two, and a fall for one; the modes of injury were unknown for two patients. The mean Glasgow Coma Score on initial evaluation was 6.7; all of the patients scored <=8. The computed tomographic scans of the head obtained at admission demonstrated a subdural or epidural hematoma in seven patients, >=1 cerebral contusions in six patients, cerebral swelling in three patients, and a subarachnoid hemorrhage in two patients. Operative intervention before the study occurred in six patients, each of whom underwent evacuation of a subdural or epidural hematoma. In addition, an ipsilateral decompressive craniectomy was performed on one patient.

Patient	Age (yr)	Sex	Mode of Injury	Glasgow Coma Scale Score	Computed Tomographic Findings	Intervention
1	50	M	Fall	5	Right frontoparietal subdural hematoma; right temporal contusion	Evacuation of right subdural hematoma
2	22	M	Assault	7	Right frontal and parietal contusions; right subdural hematoma and subarachnoid hemorrhage; left posterior fossa subdural hematoma; left frontal and temporal contusions	Evacuation of right subdural hematoma and decompressive craniectomy
3	27	M	Motor vehicle accident	5	Left thalamic hemorrhage; left temporal contusion; bilateral occipital contusion; diffuse swelling	None
4	17	M	Bicycle accident	7	Right temporoparietal epidural hematoma	Evacuation of epidural hematoma
5	19	M	Motor vehicle accident	4	Bilateral parietal contusions; mild diffuse swelling	None
6	74	F	Unknown	8	Left frontoparietal subdural hematoma	Evacuation of left subdural hematoma
7	52	M	Assault	8	Right subdural hematoma; right diffuse swelling	Evacuation of right subdural hematoma
8	44	M	Unknown	7	Left frontal epidural hematoma	Evacuation of left epidural hematoma
9	24	M	Motor vehicle accident	8	Right frontotemporal contusion	None
10	28	F	Bicycle accident	8	Right frontoparietal subdural hematoma (thin); right frontal and temporal contusions; subarachnoid hemorrhage	None

TABLE 1. Characteristics of Patients

Analysis of dynamic cerebral autoregulation requires a perturbation in systemic blood pressure to evoke the autoregulatory response while continuously recording the ABP and the MCAV bilaterally (4). In our patients, the ICP was also continuously recorded and the CPP, rather than the ABP, was used in the calculation of the autoregulatory index. This was achieved through the use of a measurement protocol, in which conventional large thigh blood pressure cuffs were wrapped around each upper thigh. The outlet ports of the cuffs were modified by the addition of large-bore tubing, which allowed rapid inflation and deflation. These cuffs were inflated to 30 mm Hg above systolic blood pressure for 4 minutes. Rapid deflation was then achieved by pulling a seal from both outlet ports simultaneously. Thigh cuff pressure dropped below diastolic pressure within 200 milliseconds and resulted in an abrupt but mild drop in mean systemic blood pressure. The blood pressure remained at a decreased level for<30 seconds before cardiovascular reflexes began to restore it to baseline. Full restoration to predrop levels was usually

complete within 1 to 2 minutes.

The dynamic cerebral autoregulatory response was analyzed by observing the relative changes in the CBF, through the MCAs bilaterally, immediately after the blood pressure drop. The relative changes in the CBF were obtained by recording relative changes in the MCA spectral outline using TCD. A 2-MHz pulsed-range gated doppler instrument (Model TC2-64B; EME, Uberlingen, Germany) was secured over each temporal window by means of a headband. The MCA trunk was identified through the use of previously described methods (1, 5). The doppler spectra were monitored continuously to detect artifact or poor signal. The spectral outline of the MCA signal, which corresponds to the blood flow velocity at the center of the artery, was taken as the maximal velocity. Radial artery cannulas and pressure transducers were used to record blood pressures, which were referenced to the level of the external auditory meatus. Patients were tested with 0 to 10 degrees of upper body elevation. Camino subarachnoid fiberoptic catheters were used to record the ICP (Camino Laboratories, San Diego, CA). The ET CO_2 was measured using a Datex infrared CO_2 monitor, Model 223 (Datex Corp., Tewksbury, MA). Simultaneous recording of maximal velocity in both MCAs, as well as the radial ABP, ICP, and ET CO_2, was performed. All of the parameters were taken as analog signals and processed through an analog-to-digital converter. These signals were sampled at a rate of 50 Hz and continuously output to an IBM AT-compatible 386 computer for storage and subsequent analysis.

Each patient underwent autoregulation testing at normoventilation; testing was then repeated at moderate hyperventilation. Testing was accomplished by means of four transient drops in blood pressure during normocapnia and four drops during hypocapnia, after a 10-minute interval for stabilization of the pCO_2. Arterial blood was sampled, and arterial pCO_2 and pH values were measured by means of a blood gas analyzer during normocapnia and again during hypocapnia. The ventilatory rate was adjusted appropriately to attempt to provide a 10-mm Hg drop in pCO_2. At the conclusion of the testing, the ventilator was returned to its original setting.

Data analysis

Data were analyzed off-line by means of an IBM AT-compatible 386 computer and customized software. Each of the four blood pressure drops during normocapnia and hypocapnia was initially screened, and several slow drops, which occurred for >4 seconds and which indicated inadequate deflation of the blood pressure cuff, were omitted because of the likelihood of an autoregulatory response that began during the change in blood pressure. The tracings were digitally filtered for analyses by means of a low-pass filter(0.3 Hz). The baseline values for the ABP, MCAV, ICP, CPP, and ET CO_2 were obtained during the 5 seconds immediately before the blood pressure drop. The change in each parameter was measured during the 1st 5 seconds immediately after the drop. The rate of regulation (RoR) was calculated by means of the following equation: RoR = ([DELTA]MCAV/[DELTA]time)/[DELTA]CPP. The RoR, therefore, represents the initial slope of the change in estimated cerebrovascular resistance (CVR) during the 1st 5 seconds of the autoregulatory response. The ET CO_2 begins to increase, [almost equal to]10 seconds after the cuff release, as a result of the return of CO_2-rich blood from the legs. There is a small secondary increase in MCAV that occurs after the CO_2 increase. Because the RoR is calculated during the 1st 5 seconds of the response, it is not effected by the CO_2 change. The mean values for both MCAVs and the ABP, ICP, CPP, ET CO_2, and RoR were calculated from the multiple tests during normocapnia and hypocapnia in each patient.

The CO_2 reactivity was determined for both MCAs from each patient. This value was calculated by dividing the percentage decrease in MCAV between normocapnia and hypocapnia by the change in the ET CO_2 during this period. Data were analyzed for each hemisphere (MCA territory) separately. All of the values are given as mean ± standard deviation. Statistical comparisons were done using Student's two-tailed t test, and significant differences were considered at the $P < 0.05$ level.

RESULTS

The values for the arterial CO_2 tension, ABP, CPP, and ICP during normocapnia and during hypocapnia are shown in Table 2. Moderate hyperventilation caused a significant ($P < 0.001$) reduction of pCO_2. This was verified with continuous ET CO_2 measurements (data not shown), which showed a comparable 10-mm Hg reduction in CO_2 with hyperventilation. Arterial pH values increased significantly($P < 0.01$) from 7.42 ± 0.04 to 7.51 ± 0.04 pH after hyperventilation. The ABP, CPP, and ICP did not change significantly.

	CO_2	ABP	CPP	ICP
Normoventilation	36.8 ± 5^b	94 ± 13	80 ± 15	14 ± 6
Hyperventilation	27.5 ± 3^b	92 ± 16	81 ± 18	11 ± 5

[a] CO_2, carbon dioxide; ABP, arterial blood pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure. All data ± standard deviations.
[b] Significantly different ($P < 0.001$).

TABLE 2. Physiological Parameters *a*

The MCAVs, as measured by TCD, are shown in Table 3. During normocapnia, the mean velocities in the right and left MCA were not significantly different from one another. However, hemispheres with mass lesions (subdural or epidural hematoma) had MCAVs that were significantly lower ($P < 0.05$) than the MCAVs from the hemisphere without a mass lesion in the same patient. Hyperventilation produced a mean reduction in MCAVs for all hemispheres of 12 ± 5.4 cm per second. The mean velocity for MCAs in hemispheres with mass lesions was also lower after hyperventilation (43 versus 56 cm/s), but this difference was not significant.

	Normoventilation	Hyperventilation
Hemisphere		
All	56 ± 12.3	43 ± 12.5
Right	53 ± 8.8	42 ± 9.5
Left	58 ± 15.5	45 ± 15.4
Mass lesions		
Side of mass	51 ± 10.1^b	41 ± 12.5
Opposite mass	62 ± 16.1^b	46 ± 17.1

[a] Values given in centimeters per second ± standard deviation.
[b] Significantly different ($p < 0.05$)

TABLE 3. Middle Cerebral Artery Velocities *a*

The blood pressure drops achieved by the release of the thigh cuffs resulted in lowering of the blood pressure by nearly identical amounts during normoventilation and hyperventilation (Table 4). The time needed for the blood pressure to recover from the perturbation was also similar during normoventilation and hyperventilation. The MCAVs were reduced coincident with the ABP drops. During normoventilation, the mean reduction in MCAV for all of the hemispheres was 16.1 ± 4.3 and 11.5 ± 4.8 cm per second during hyperventilation. The percentage decrease was similar, relative to the baseline velocity, before and during hyperventilation (Table 4). Figure 1 illustrates an example of four autoregulation tests before and after hyperventilation and the average values for the four tests, which show the improvement in autoregulation.

	Normoventilation	Hyperventilation
Change in ABP (mm Hg)	28 ± 5.4	27 ± 6.1
Duration of drop (s)	49 ± 24.2	49 ± 23.2
% Change in velocity (cm/s)	29 ± 6.6	26 ± 8.9

[a] ABP, arterial blood pressure. All data ± standard deviations.

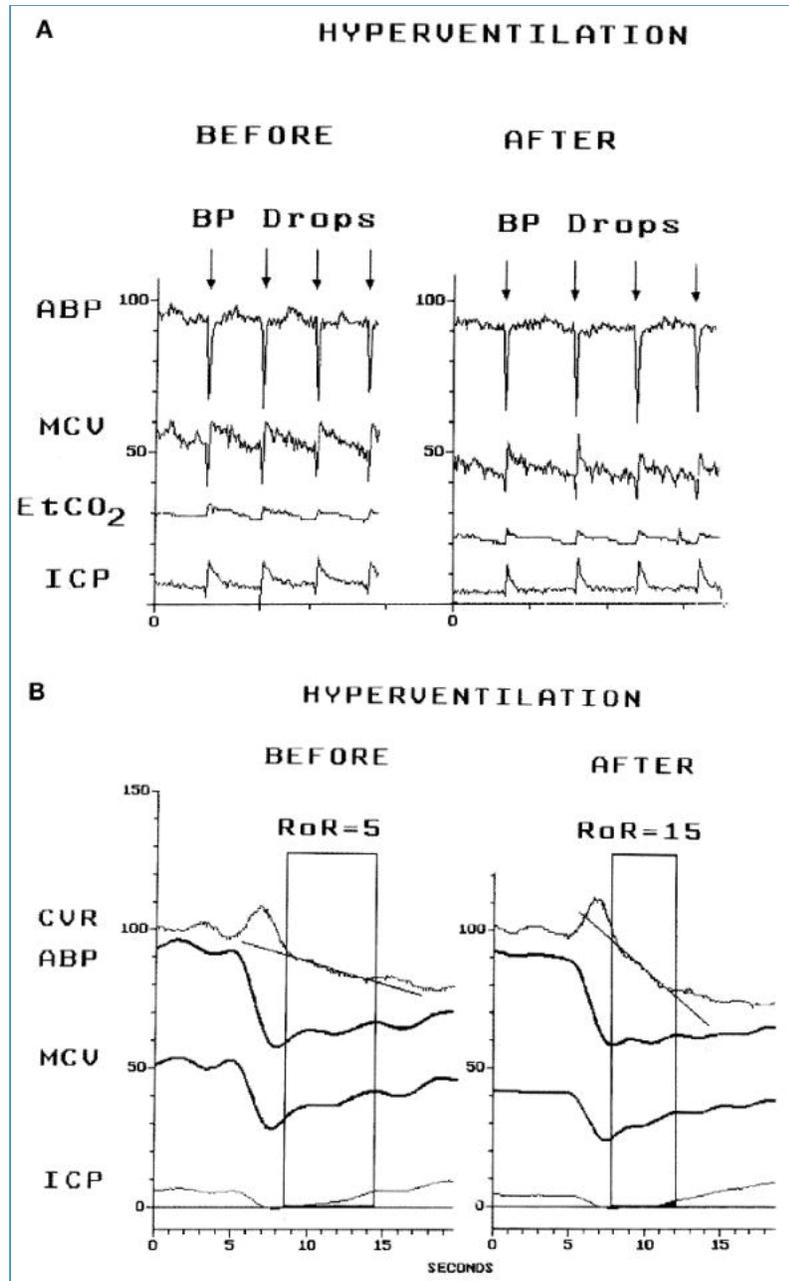**TABLE 4. Changes during Blood Pressure Drops** *a*

FIGURE 1. Illustration of an example of four autoregulation tests before and after hyperventilation (*A*) and the average values for the four tests, which show the improvement in autoregulation induced by hyperventilation (*B*).*BP*, blood pressure. The CVR is estimated on the basis of the MCAV rather than the CBF.

The mean value for the CO_2 reactivity of all of the hemispheres studied was 2.7 ± 1.5% per mm Hg, which is within the normal range(2-4%/mm Hg CO_2) (29). The RoR for all of the patients, calculated from the change in velocity relative to the CPP during the 1st 5 seconds after a blood pressure drop, is shown in Figure 2. During normocapnia, the mean RoR was 11.4± 5.2% per second. The range was 2.7 to 21.7% per second, with no identifiable relation to any parameter examined, including the presence or absence of a mass lesion. After hyperventilation, the RoR improved significantly (*P* < 0.001) to 17.7 ± 5.9% per second. The absolute increase in RoR averaged 6.3 ± 4.6% per second, with a range of improvement from 0.3 to 17% per second. The pooled variance found with repeated measurements of RoR in the same patient and under the same conditions was 2.69% per second. Figure 2 also demonstrates that the change in RoR was not related to the initial RoR, i.e., patients with a low RoR during normoventilation sometimes improved a little but usually improved significantly and sometimes dramatically. This was also true for patients with an initially high RoR, in whom some values improved a little and some dramatically.
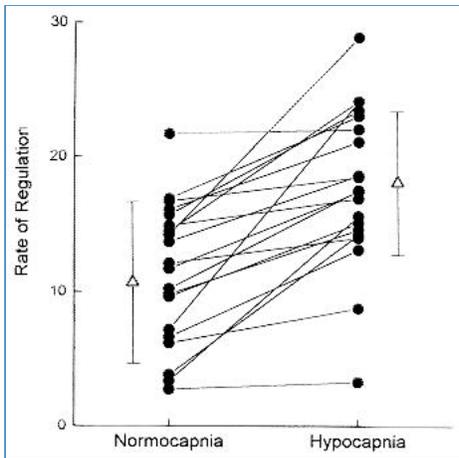
FIGURE 2. Illustration of the change in the RoR (index of autoregulation) in each individual MCA territory, induced by hyperventilation(hypocapnia) ($P < 0.001$ by t test). *Triangles* indicate means; *error bars* denote standard deviations.

There was a significant correlation ($r = 0.46$, $P < 0.05$) between CO_2 reactivity and change in RoR (Fig. 3). There was no significant correlation ($r = -0.23$, $P = 0.33$), however, between the change in pH value after hyperventilation and the improvement in RoR (Fig. 4). We also examined the relationship between the initial RoR (at normocapnia) and the CPP. There was a slight inverse relationship between the initial RoR and the CPP, but there was no significant correlation ($r = -0.26$, $P = 0.27$) (Fig. 5). This analysis demonstrates that autoregulation was impaired in some patients, despite an adequate CPP. We also performed a regression analysis between the initial RoR and CO_2 reactivity. There was no significant correlation between these parameters ($r = -0.14$, $P = 0.56$)(Fig. 6). This analysis revealed that patients could have a marked impairment in autoregulation despite a normal CO_2 reactivity. However, we did not observe patients with absent CO_2 reactivity and normal autoregulation.
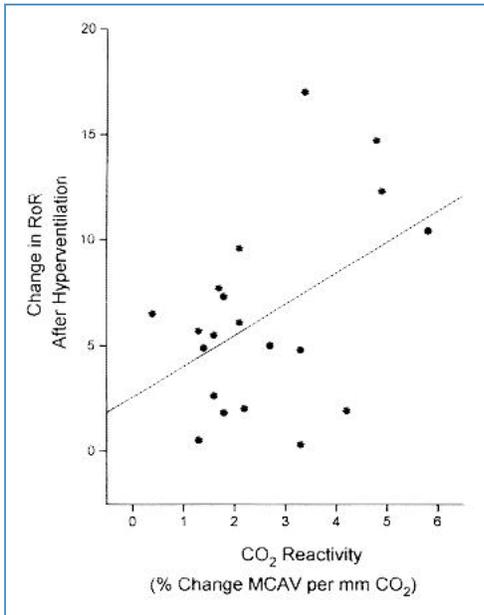

FIGURE 3. Regression analysis illustrating the significant correlation between the CO2 reactivity in each MCA territory and the improvement in autoregulation indicated by the change in the RoR after hyperventilation ($P = 0.042$, $r = 0.46$, $n = 20$, $y = 2.5 + 1.5$ x).
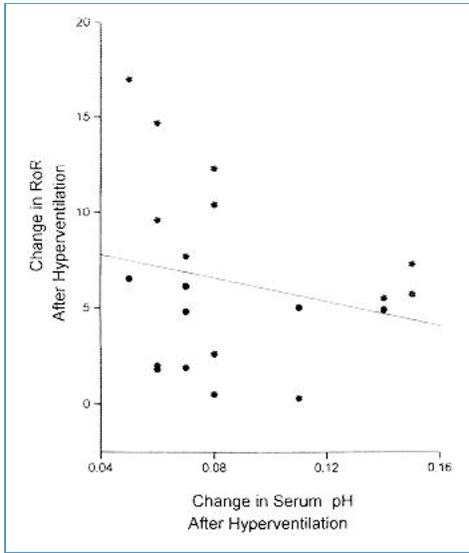
FIGURE 4. Regression analysis indicating no significant correlation between the change in the serum pH value and improvement in autoregulation after hyperventilation ($P = 0.34$, $r = -0.23$, $n = 20$, $y = 9.0 - 30.8\ x$).
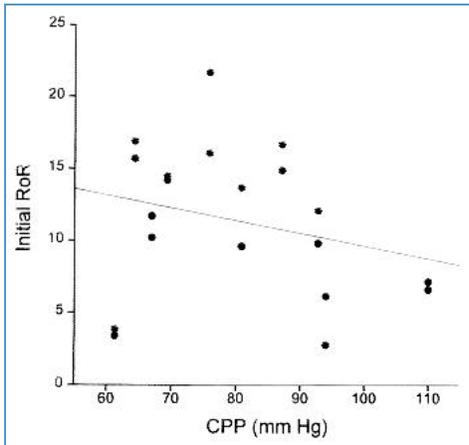

FIGURE 5. Illustration of the relationship between the initial RoR and the CPP. There was a slight inverse relationship but no significant correlation ($P = 0.27$, $r = -0.26$, $n = 20$, $y = 18.4 - 0.08\ x$). This analysis reveals that autoregulation was impaired in some patients, despite adequate CPP.
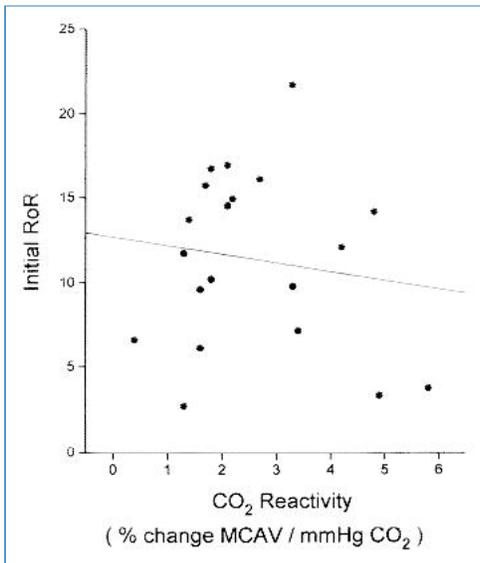
FIGURE 6. Illustration of the relationship between the initial RoR and the CO2 reactivity. There was no significant correlation between the two measures (P = 0.6, r = -0.14, n = 20, y = 12.7 - 0.5 x). There were examples of values that indicated an intact CO2 reactivity with severely impaired autoregulation, but we did not observe autoregulation values in the normal range with absent CO2 reactivity.

DISCUSSION

The present study demonstrates that dynamic autoregulation is impaired after severe head injury. During normocapnia, the average RoR in this group of head-injured patients was 11.7% per second, which is substantially lower than values reported for healthy volunteers (20 ± 3%/s)(4). We demonstrated a significant temporary improvement in dynamic autoregulation in this group of patients by use of transient moderate hyperventilation. Lowering the pCO_2 from a baseline value of 37 to 28 mm Hg resulted in improvement in the index of dynamic autoregulation from 11.7% per second, which is moderately impaired, to 17.7% per second, which is in the normal range. These values for autoregulation represent the average for the group of patients; the data obtained from both hemispheres were used to represent each patient. Figure 2 illustrates the change in autoregulation induced by hyperventilation in each cerebral hemisphere. The improvement in autoregulation represents true improvement of values in impaired hemispheres rather than merely an improvement in values that were previously healthy, as illustrated by Figure 2.

The method of analyzing dynamic cerebral autoregulation by use of TCD is based on the ability of TCD to measure relative changes in blood flow through the MCA during the autoregulatory response to rapid induced changes in the ABP (2, 4, 6, 35, 36, 46). Several investigators, who used different methodologies, confirmed that the MCA diameter remains constant during moderate changes in the ABP. Therefore, changes in velocity reflect relative changes in flow through the MCA trunk (6, 20, 24, 36). We previously compared internal carotid blood flow, measured by means of an electromagnetic flowmeter, to MCAV during the autoregulation test used in the present study; we found no difference in the two parameters (36). The TCD method for measuring CO_2 reactivity has also been validated (8, 21, 25, 45). In healthy individuals with intact autoregulation, a reduction in the ABP leads to dilation of the distal cerebral vessels, not the MCA trunk, and a decrease in CVR (2). This response leads to a rapid restoration in the CBF before the ABP has returned to baseline. The rate of change of the estimated CVR is derived from the change in the CBF relative to the change in the ABP. Full restoration of the CBF would theoretically occur if the change in the CVR equaled the change in the ABP. The RoR is the measure of this dynamic component of cerebral autoregulation and is defined mathematically as RoR =([DELTA]CVR/[DELTA]time)/[DELTA]ABP (4). In other words, the RoR is the percentage change in velocity or flow toward baseline that occurs per second during the interval measured. For a normal individual at normocapnia, the RoR is [almost equal to]20% per second (or RoR = 0.20)(4). For our patients, we obtained continuous ICP recordings and therefore substituted the CPP for the ABP in the calculations.

The measurement of dynamic cerebral autoregulation by the use of TCD has several advantages over static measurement techniques that use radioactive xenon. The TCD method does not require radioisotopes and does not require the use of vasoactive medications to cause a blood pressure perturbation to evoke the autoregulatory response. Moreover, evaluation of the dynamic autoregulatory response permits measurement of the response latency, which may prove to be important in head-injured patients. We recently compared the relationship between static and dynamic autoregulation in patients with progressive impairment in autoregulation caused by the administration of anesthetic agents (46). In this study, static testing was accomplished by increasing the blood pressure with phenylephrine and measuring the relative blood flow changes by use of TCD. Abolished autoregulation detected by static testing was also abolished when evaluated by dynamic testing. We did not find any examples in which static autoregulation was intact and dynamic autoregulation was absent.

The mechanism of the improvement in autoregulation induced by mild hyperventilation is not clear. Possible mechanisms to account for this improvement may include an improved CPP, alterations in the pH value of the cerebrospinal fluid, and increased vascular tone (2, 5, 14, 15). In head-injured patients, either a low ABP, or a high ICP, or a combination of these can lead to a CPP that is reduced below the level at which the autoregulatory mechanism is effective. In such cases, the autoregulatory mechanism may be intact and will function if the CPP can be restored. Autoregulation also may be impaired after head injury from unknown causes and may not function despite an adequate CPP (25, 28). If hyperventilation significantly reduced the ICP, then an increase in the CPP might contribute to an improvement in autoregulation. We measured the CPP at both levels of pCO_2 during autoregulation testing and found no significant differences that could account for the observed improvement. The average CPP at both levels (80 mm Hg) should be in the range in which autoregulation is effective (40). During our testing, however, at both CO_2 levels, the nadir of the drop in blood pressure during the dynamic testing may well have reached the lower limits of autoregulation.

Another possible mechanism for improvement in autoregulation may involve the effect of hyperventilation on metabolic mediators. For example, hyperventilation increases adenosine levels in the brain, which may play a role in cerebral autoregulation (49, 50). The shift in acid-base balance in the cerebrospinal fluid induced by hyperventilation could theoretically effect the efficiency of the autoregulatory response. The arterial blood gas pH values increased from 7.42 ± 0.04 to 7.51 ± 0.04 pH after hyperventilation, but there was no demonstrable relation revealed by

regression analysis between autoregulation and the change in pH values. Arterial blood gasses were drawn >=10 minutes after ventilator changes were made. We assumed that the cerebrospinal fluid pH values would be similar to the blood pH values under steady-state conditions with mechanical ventilation. Muizelaar et al. (32) measured blood and cerebrospinal fluid pH values before and after hyperventilation in rabbits and found that an equal change was induced in each with acute hyper-ventilation. A more likely mechanism for the improvement in autoregulation demonstrated in our study was an improvement in the vascular tone cause by vasoconstriction induced by hyperventilation (2, 14, 15). Increased arterial vascular tone may improve the efficiency of the autoregulatory response by changing the set point of the regulating vessels to a more favorable position for affecting a rapid change in vascular resistance. We found a positive correlation between the CO_2 reactivity and improvement in the autoregulation observed in each individual MCA territory. This finding suggests that the degree of vasoconstriction induced by hyperventilation influences the magnitude of the improvement in the autoregulatory response.

In accord with previous studies, we did not find a close relationship between CO_2 reactivity and autoregulation after head injury (12, 13, 17, 18). We observed that autoregulation could be impaired despite a normal CO_2 reactivity, but we did not observe values that indicated that CO_2 reactivity was abolished despite normal autoregulation. We previously reported that impairment in autoregulation is highly correlated with impairment in CO_2 reactivity in patients with cerebrovascular occlusive disease, in contrast with head-injured patients (35). The most likely explanation for the correlation between autoregulation and CO_2 reactivity in occlusive disease is that the CPP in the MCA territory is reduced below the level at which autoregulation functions effectively. At a low CPP, CO_2 reactivity is also impaired, because the cerebral resistance vessels are already dilated. After head injury, autoregulation and CO_2 reactivity can also be simultaneously impaired as a result of a low CPP. We demonstrated in this study, however, that autoregulation can be impaired in some severely head-injured patients with a relatively high CPP(see Fig. 5). This finding seems to indicate that another mechanism may be responsible for impaired autoregulation in some of these patients (23, 28). Miller et al.(28) demonstrated experimentally that repeated brain compression could abolish autoregulation, presumably by induction of cerebral ischemia. It is likely that ischemic injury could cause impairment in autoregulation in head-injured patients despite an adequate CPP.

Paulson et al. (39) demonstrated that moderate hyperventilation by use of xenon washout techniques improved static autoregulation in patients with impaired autoregulation resulting from strokes and tumors. Using a similar methodology, Cold et al. (12) measured autoregulation in head-injured patients by obtaining static CBF measurements before and after angiotensin infusion at two different CO_2 levels. Autoregulation was found to be preserved at a moderately reduced pCO$_2$ (34 mm Hg) but was impaired when pCO$_2$ was reduced to low levels (23 mm Hg) by more intense hyperventilation (12). The study of Paulson et al. (39) is thus consistent with our findings, and the studies together suggest that autoregulation is improved with moderate hyperventilation, when either static or dynamic methods are used to evaluate the autoregulatory response.

Animal studies have not completely clarified the effect of CO_2 levels on autoregulation. Ekstrom-Jodal et al. (16) demonstrated that hypocarbia improved the autoregulatory response to induced hypertension, and others demonstrated that acute hypercarbia caused a loss of autoregulation to elevations in blood pressure (41). In contrast, however, Artu et al. (7) showed that hypocarbia did not affect the lower limit of autoregulation. Symon et al.(48) showed that hypercarbia did not cause a loss of autoregulation in response to increased pressure. These discrepancies may, in part, reflect the variations in experimental design of these studies and may also suggest that the effect of CO_2 on autoregulation is complex and may be influenced by multiple other factors.

The purpose of this study was to test the hypothesis that moderate hyperventilation would transiently improve the autoregulatory response in head-injured patients. The findings of this study are significant, because they help to define the pathophysiological basis of impaired autoregulation after head injury. Improvement of cerebrovascular tone seems to be effective in improving the autoregulatory response. These results, however, do not justify the use of prolonged moderate hyperventilation for this purpose. Although moderate hyperventilation improved autoregulation temporarily in our patients, longer periods of hyperventilation may not facilitate a sustained improvement. Previous studies on the effect of hyperventilation on vasoconstriction of cerebral vessels suggest that the effect of hyperventilation is short lived. Muizelaar et al. (32) demonstrated that the cerebral vasoconstriction produced initially at the onset of hyperventilation is temporary and that the vessels return to their baseline diameter within 20 hours, despite continuous hyperventilation. If the improvement in autoregulation is the result of an improvement in vascular tone induced by hypocapnia, then this improvement may be lost if the vascular tone returns to baseline.

The transient improvement in autoregulation produced by moderate hyperventilation does not indicate that hyperventilation has an overall beneficial effect in head-injured patients. Moreover, the improvement in autoregulation by hyperventilation is achieved at the expense of a lower CBF (39, 40). In addition to the possible transient nature of the effect, several investigators have demonstrated that more intense hyperventilation may cause cerebral ischemia (10, 47). Moreover, a recent prospective randomized trial of chronic hyperventilation for 5 days in severely head-injured patients did not show a benefit of this treatment. There was a worse outcome at 3 months in a subgroup of patients (31).

Other similar strategies to improve autoregulation may have more prolonged effects. For example, the intracellular buffer tromethamine may also induce moderate vasoconstriction by a pH-dependent mechanism that is similar to that of hyperventilation but is longer lasting (31, 42, 51, 52). Barbiturates also can induce cerebral vasoconstriction by a different mechanism, primarily by the reduction in cerebral metabolism (11). Further work is needed to assess whether these compounds or others can induce similar improvements in autoregulation. The simplicity and reliability of the TCD method to measure autoregulation will, it is hoped, lead to further study of impaired autoregulation in head injury and other conditions.

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COMMENTS

This report from the group that developed transcranial doppler technologies in head injury is of considerable interest. Although we do not know, in an absolute sense, whether the restoration of the autoregulatory response is important clinically, it is likely that it is. Thus, a relatively simple methodology that can improve the regulatory response of the cerebral circulation is welcome. The authors rightly caution concerning the potential risks of hyperventilation, although I think that these concerns, in instances in which the pCO_2 is maintained above 30 mm Hg, are uncompelling. These observations, however, will only serve to sharpen the debate concerning the role of hyperventilation and how it should be used in the treatment of patients with severe brain injuries. Because the technology applied here is global and tells us nothing about cerebral metabolism, it will not directly influence the opposing views regarding the adverse consequences, if any, of moderate hyperventilation. It does serve, however, to emphasize the need for regional flow and metabolic studies, in both animal models and humans, so that we may better understand the pros and cons of moderate hyperventilation.

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Compared to the old methods (i.e., the use of transcranial doppler in lieu of radioactive tracers and the use of the blood pressure cuffs in lieu of vasoactive drugs), Newell et al. use elegant techniques to test autoregulation. Nevertheless, despite the greater ease of the measurements, I do not foresee a real clinical applicability for autoregulation testing. As the authors noted, many of our management strategies act through or are influenced by autoregulatory mechanisms but they themselves do not give us an indication of how knowledge of the status of autoregulation might be useful. Although in rare instances one can use autoregulatory vasoconstriction with higher blood pressure to control high intracranial pressure (2), the general rule is to avoid arterial hypotension irrespective of whether autoregulation is intact (1). Despite these comments, this article is important because it generally deepens our insight into the pathophysiological features of severe head injury. Moreover, I particularly like the thoughtful discussion of the effect of hyperventilation; an "improvement" in autoregulation does not necessarily mean that sustained hyperventilation is good for all of our patients.

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The authors pursued, with care and elegance, a complex physiological experiment. Although the authors concluded that hyperventilation improves cerebral autoregulation, their experiment does not suggest that prolonged hyperventilation should be used to improve the outcome of traumatic brain injury nor do their data suggest improvement in cerebral autoregulation.

In interpreting their findings, it might be useful to take a macroscopic view of the data and then look at them in more detail. The cerebral autoregulatory response is designed to maintain relatively stable and normal levels of cerebral blood flow (CBF) across a wide range of pressures. The essential mechanism is one of changing cerebrovascular resistance (CVR) over a pressure range by varying vasodilation and constriction.

The authors attempted to quantify rates of vasoconstriction and dilation by estimating the slope of the resistance change that occurred during the 1st 5 seconds of recovery of CBF after an acute reduction in arterial blood pressure(ABP) and cerebral perfusion pressure (CPP). This estimate of CVR was normalized to the middle cerebral artery velocity (MCAV) baseline before each hypotensive event. In other words, the baseline vasoconstriction that was extant after hyperventilation was induced, before the hypotension, still yielded a CVR estimate of 100%, even though it was clearly higher during hypocapnia ([almost equal to]130% of mean, normocapneic levels). The authors relate all of the subsequent measures and changes to the conditions before the hypotensive perturbation.

Broadly speaking, it is important to note that hyperventilation reduced MCAVs in all of the patients by >=20%. If the MCAV is to be taken as proportional to the CBF, then the CBF was not normal at the outset and hyperventilation reduced it further by a large fraction. Second, what "improved" after hyperventilation was the initial rate of return toward this (abnormal) baseline level; it seemed to be faster on the basis of the estimated CVR than it did in the nonhyperventilated circumstance. We do not know the time required for MCAV (CBF) to return to baseline, nor do we know the CVR. Because CBF (MCAV) was only 60 to 80% of baseline, the overall system did not "improve" in any important sense. A derived index seemed to return to its baseline a bit faster. Why? Because the baseline conditions varied (see above) with each test, and because the amount of vasoconstriction available is limited.

Under most circumstances, the CVR is minimal at a CPP of 50 to 60 mm Hg and nearly maximal at a CPP of 100 to 120 mm Hg (near maximal vasoconstriction). There is only a small fraction of vasoconstriction left to be attained at levels above this. In other words, once the vessels vasoconstrict, the amount of vasoconstriction left is limited. Hypocapnia forces vasoconstriction, which is why it reduces the CBF. This is in contradistinction to a high CPP or mannitol, both of which "allow" vasoconstriction with a higher or maintained blood flow. The decrement in ABP used by the authors was a vasodilatory stimulus. What the authors concluded that they observed was a relative increase in the rate of vasodilation after the vessels had been forced into a state of constriction by hypocapnia. The measure of the CVR used by the authors is insensitive, because it lacks an absolute reference. They may well have concluded the opposite if their CVR estimates had been based upon the MCAV before the first normocapneic, hypotensive event, rather than related to that before each separate event.

At a more microscopic level, if one examines Figure 1B, one notes that as the ABP rapidly declined, the CVR initially increased. This increase represents a passive collapse of the vasculature that mathematically converts to an increase in resistance. The resistance peaked and began to decline at a variable rate thereafter. The time from the decrement in ABP(when the CVR began to increase) and the peak of the CVR, after which it decreased, represents the latency of the vasculature beginning to dilate. This is another measure of the autoregulatory response. It should be pointed out that in Figure 1B, the time for this to occur before hyperventilation was [almost equal to]1.5 seconds and that this time increased to [almost equal to]2 seconds after hyperventilation had been induced. It seems that the vasculature is more sluggish after hyperventilation than before.

A side-by-side comparison of the rate of return of the MCAV toward baseline suggests that hyperventilated patients show a slower return to baseline than do patients in the normocapneic state. This is even in the face of a lower baseline level; i.e., the CBF did not have as far to go but still got there more slowly. These interpretations suggest an overall dampening, not enhancement, of the autoregulatory response. It can be suggested that the reason that the "mechanism of the improvement in autoregulation induced by mild hyperventilation is not clear" is that cerebral autoregulation has not truly improved.

In summary, the model and data are wonderful; the conclusions are less so. Hypocapnia decreased the CBF to 75% of baseline, accentuated the drop in the CBF caused by hypotension by another 26%, and probably slowed the rate of normalization of the CBF as the hypotension resolved. In no way can these observations be construed as "improvement" in the system.

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Key words: Autoregulation; Cerebral blood flow; Head injury; Hyperventilation; Transcranial doppler ultrasonography

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IMAGE GALLERY

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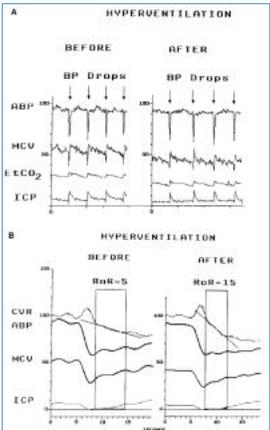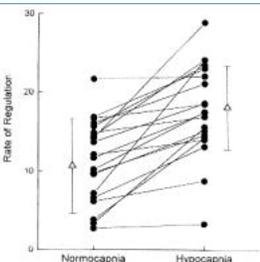

☐ Table 1

☐ Table 2

☐ Table 3

☐ Table 4

☐ Figure 1

☐ Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

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