Acta Neurochir (Wien) (1997) 139: 804–817

Acta Neurochirurgica

Evaluation of Hemodynamic Responses in Head Injury Patients with Transcranial Doppler Monitoring

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Summary

Transcranial Doppler (TCD) can monitor middle cerebral artery (MCA) velocity which can be recorded simultaneously with other physiologic parameters such as end tidal (Et) CO_2, arterial blood pressure and intracranial pressure (ICP), in head injured patients. Relative changes in MCA velocity can be used to reflect relative MCA blood flow changes during ICP waves, and also to evaluate cerebral autoregulation, CO_2 reactivity and hemodynamic responses to mannitol and barbiturates. The utility and practicality of short intervals of TCD monitoring to evaluate hemodynamic resposnes, was evaluated in a group of 22 head injured patients (average Glasgow coma score 6). During ICP A waves, MCA velocity always decreased during the peak of the wave, and during ICP B waves, fluctuated synchronously with the ICP. Dynamic cerebral autoregulation, and reactivity to CO_2, were reduced within 48 hours of admission. Impaired cerebral autoregulation within 48 hours of admission did not correlate with outcome at 1 month. Mannitol infusion caused an increase in MCA velocity (15.4 ± 7.9%) which was significantly correlated to the impairment of dynamic autoregulation ($r = 0.54$, $p < 0.0001$). The MCA velocity response to a test dose of barbiturates was significantly correlated to the ICP ($r = 0.61$, $p < 0.01$) response as well as to the CO_2 reactivity ($r = 0.37$, $p < 0.05$).

Continuous MCA velocity monitoring using TCD may be useful in evaluating a variety of hemodynamic responses in head injury patients and may replace more cumbersome cerebral blood flow techniques which have been used in the past for these purposes.

Keywords: Transcranial Doppler ultrasound; head injury; autoregulation; A-waves.

Introduction

Continuous recording of blood flow velocity in the basal cerebral arteries using transcranial Doppler can provide a method to assess cerebral hemodynamics and also to evaluate relative cerebral blood flow (CBF) changes [1, 3–5, 8, 29, 33]. This technique may provide a more practical alternative to other CBF measurement methods which have been used for the assessment of responses to various therapies in patients with head injury and other neurological conditions requiring intracranial pressure (ICP) management [9, 13, 16, 26, 34, 35].

The relative changes in the middle cerebral artery (MCA) mean velocity (spectral outline) through the MCA are then used to reflect relative cerebral blood flow changes in response to end tidal carbon dioxide ($EtCO_2$), arterial blood pressure (ABP) changes (autoregulation), to mannitol infusion and in response to barbiturate therapy. Blood flow velocity changes through the MCA during fluctuations of ICP produced by routine critical care maneuvers as well as during various waves of the ICP can also be evaluated.

Knowledge of the integrity of the autoregulation may be valuable in identifying patients who may be at risk for secondary ischemia due to reduced cerebral perfusion pressure caused by increased ICP and or low blood pressure. This information could also be valuable in identifying patients with poor autoregulation who may be at risk for developing secondary hemorrhages and edema from unwanted blood pressure increases [53]. The ability to evaluate autoregulation in head injured patients noninvasively using this method, may offer additional insights into the mechanism of the impairment of this response as well as a method to assess strategies to improve autoregulation.

Clinical Material and Methods

Twenty-two patients admitted to the intensive care unit of Inselspital in Bern, Switzerland with a diagnosis of closed head injury and were included in the present study. Age range was 16–69 with a mean age of 36. Average Glasgow coma score (GCS) was 6 (range 3–10). There were 18 males and 4 females. These patients had continuous ABP, ICP, and $EtCO_2$ monitoring and were artificially ventilated during their initial hospital course. A total of 153 continuous recordings of blood flow velocity from the middle cerebral artery were made with simultaneous continuous recordings of ABP, ICP, and $EtCO_2$. These recordings were repeated serially, usually on a daily basis ranging between 1 and 15 days. Recordings were usually taken from both MCA's of the same patient separately during the monitoring session. Monitoring was performed for variable time periods, usually for periods of 1 to 3 hours.

Middle cerebral velocity signals were recorded through a transtemporal window. A 2 MHz pulsed range gated Doppler transducer, fixed with a head band was used for TCD monitoring (Eden medical electronics Uberlingen, Germany). Patients were usually sedated or chemically paralyzed therefore movement and probe dislodgment difficulties were minimal. Satisfactory signals were obtained in 100% of the subjects. Signals were recorded from the MCA trunk at a depth between 50–60 mm which was located using previously accepted criterion [1, 2]. The spectral display was continuously observed to ensure signal consistency. The spectral outline which corresponds to the maximum blood flow velocity (V_{max}) at the center of the artery was then taken as an analog signal and processed with the 3 other analog signals (ABP, ICP, $EtCO_2$) through an analog to digital converter (see Fig. 1). This value was used as a relative index of flow through the MCA. Blood pressure monitoring was accomplished using standard intra-arterial catheters and pressure transducers. Intracranial pressure was monitored using an epidural pressure recording device (Gealtec Ltd. Dunvegan, Scotland). Continuous $EtCO_2$ signals were obtained using side port sampling with an infrared CO_2 detector. Digital signals from the 4 different modalities were then analyzed using custom software.

Reactivity to CO_2 was tested by inducing a step decrease in arterial CO_2 concentration (8–10 mm Hg) by hyperventilation. This was accomplished by temporarily disconnecting the patient from the ventilator and hand ventilating using a ventilation bag, for at least 2 minutes which was adequate for stabilization of the response. The values from a stable recording period from before and after the manipulation were then averaged, and the relative response (percentage blood flow velocity change from the baseline, per mm CO_2 change) was calculated.

Table 1. *Explanation of Commonly Used Terms*

Rate of regulation (RoR)	Measure of the effectiveness of the autoregulatory response
CO_2 reactivity	Percentage change in cerebral blood flow (as measured by % change in MCA velocity) per mm change in CO_2
Cerebrovascular resistance (CVR)	CVR = cerebral perfusion pressure/cerebral blood flow

Autoregulation was tested according to the method of Aaslid *et al.* [4, 5] by inflating leg cuffs around both thighs to a supra systolic blood pressure for a period of 2 minutes and then rapidly deflating them, inducing a systemic blood pressure drop. A single thigh cuff was used in one patient who had sustained a leg fracture on the other side. We did not observe any clinically evident venous thromboses in the patients tested, before or after the testing. The usual blood pressure drop was between 15–25 mm Hg following release of the cuffs. Most often the blood pressure began returning toward resting levels within 10 seconds and was near or at normal levels within 30–60 seconds. The theoretical risk of cerebral ischemia was therefore low. The efficacy of the dynamic autoregulatory response was calculated according to the method of Aaslid *et al.* [4]. The relative change in CBF (evaluated by the change in mean MCA velocity) was observed following the sudden blood pressure decrease and recovery. Relative changes in velocity in comparison to relative changes in cerebral perfusion pressure (CPP) were examined in reference to their control values immediately preced-

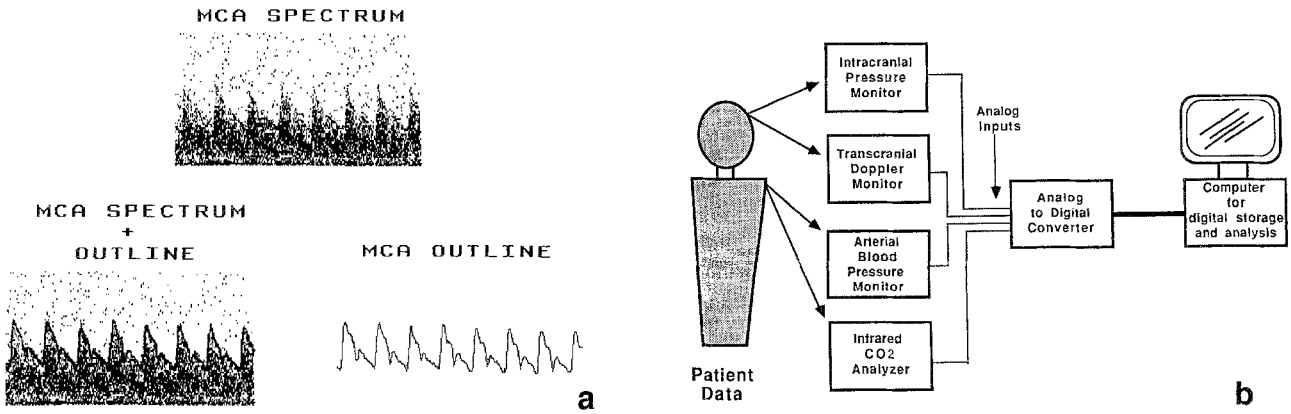


Fig. 1. (a) This figure illustrates the derivative of the MCA outline or V_{max}. The middle cerebral artery spectrum is generated by a spectrum analyzer and then assigned an outline along the maximal spectral tracing. This maximal spectral outline is then taken as an analog signal and can be recorded continuously as a trend. The spectral outline or V_{max} corresponds to the flow velocity at the central portion of the artery during laminar flow. (b) This figure illustrates the method by which multiple signals are acquired from the patient as analog data then converted to digital data through an analog digital converter and stored by computer for further analysis

ing the BP drop. Relative changes in cerebrovascular resistance (CVR) were calculated by the computer for each time point by dividing CPP by MCA velocity, and then plotted alongside these values. By then observing the change in CVR following the blood pressure drop, an index of the effectiveness of the autoregulation was determined. The CVR changed in a linear fashion between 1 and 5 seconds following the blood pressure drop. A regression line was then fitted to this data and the slope of the regression line (change in CVR/change in time) gave an index of the rate of change of the CVR. This rate of change was defined as the rate of regulation (RoR). The RoR was therefore defined as the change in CVR/change in time divided by the change in CPP (see Fig. 5 a). In a previous study of a group of healthy volunteers at normocapnia, the normal value for RoR was found to be 20 ± 3 [4]. According to this definition an RoR of 20 means that 20% of the change in cerebrovascular resistance required to bring the CBF back to baseline following the blood pressure drop, occurs per second.

The cerebrovascular response to mannitol was tested by infusing 0.4 g/kg of a 20% mannitol solution intravenously, over 5 minutes. Continuous recording of all parameters were then performed for at least 20 minutes following the end of the infusion. Change in blood flow velocity was then calculated as the maximum percentage change that occurred following the infusion. This usually occurred 10 minutes after the mannitol was given. A regression analysis was performed between the percent change in MCA velocity following the mannitol infusion and the RoR which was determined before the infusion. A regression analysis was also performed between the percent change in MCA velocity following the mannitol infusion and the percent reduction in ICP.

The hemodynamic response to barbiturate infusion was assessed by rapidly infusing (over 1 minute) a loading dose (5 mg/kg) of thiopentone according to the method of Cold *et al.* [14], and observing the response in blood flow velocity, ABP, and ICP. The relative blood flow change was estimated from the percent change in MCA velocity following the infusion. Regression analyses were then performed between the percent change in MCA velocity following infusion and the percent change in ICP, and also between percent MCA velocity change following infusion, and CO_2 reactivity.

Results are expressed as mean ± standard deviation. Statistical analyses were performed using Student's non paired t-test and the Wilcoxon sum rank test. Studies were approved by the hospital institutional review board.

Results

Characteristics of the Recordings

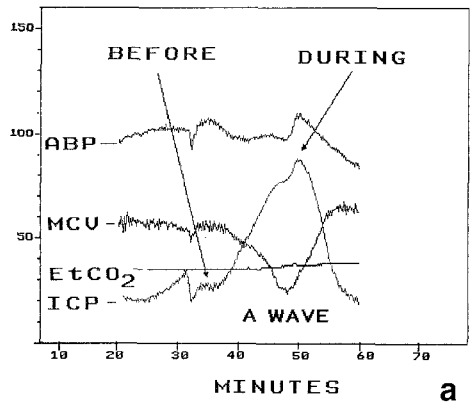
Satisfactory recordings of the middle cerebral artery were obtained in all patients. Simultaneous recording of ABP, ICP, CO_2, and MCV revealed several characteristic features depending on the interval of the recording examined. The arterial pulse wave produced a similar pulsatile wave form in the MCA velocity tracing. This is due to the relatively stiff nature of the conducting artery system which transfers most of the cardiac stroke volume directly into flow, thereby maintaining a very close pressure-flow relationship [6, 17]. When slightly longer intervals were sampled, periodic synchronous fluctuations in the ABP, MCV, and ICP recordings were seen in many patients which corresponded to the respirator frequency. The ABP change induced by the respirator normally induces a corresponding change in the MCV. The dynamic autoregulatory response is normally initiated after a delay of 1–2 seconds [4]. Therefore even when dynamic autoregulation is intact, the fluctuations in ABP produced by the respirator can produce brief transient changes in CBF which cannot be adjusted for by the autoregulation. Longer term trends were also examined which revealed characteristic findings during A waves and B waves in the ICP.

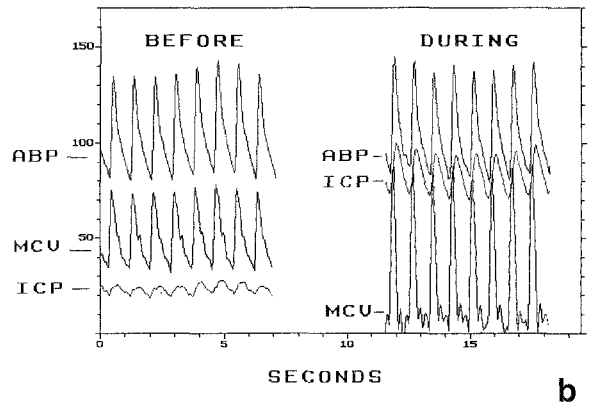
A Waves

Continuous recordings were obtained during ICP waves, characteristic of A waves, or plateau waves, described by Lundberg [30]. Seventeen waves were observed in three patients characterized by an abrupt onset of increased ICP, returning to baseline after a variable time period. The duration of the waves varied from 4 to 20 minutes and the peak ICP during the waves was 58.8 ± 14.2 mm/Hg (range 34–86). Figure 2 illustrates typical findings during A waves of the ICP. During all of the waves examined, there was a decrease in the middle cerebral velocity (MCV) during the peak of the ICP wave (mean decrease 31.7% ± 14.6) compared to the baseline value before the wave. There was also a significant ($p < 0.001$) increase in pulsatility index (systolic velocity – diastolic velocity/mean velocity) of the MCA velocity waveform observed by comparing the interval immediately preceding, to the peak of the wave (1.02 ± 0.14 to 2.22 ± 0.74). In the patients who demonstrated A waves blood pressure step changes induced by the autoregulation testing often resulted in a small ICP wave, similar to that seen with the true A waves, but much smaller in magnitude and shorter in duration. On two occasions a blood pressure drop induced by autoregulation testing resulted in true A waves. This phenomenon was not seen in patients who did not experience spontaneous A waves.

B Waves

Repeating fluctuations of the ICP occurring at a frequency between 0.5 and 2 cycles per minute have been defined by Lundberg as B waves [30]. B waves were observed in 38 of 69 of our recordings (55%) which had stable recordings for longer than 1 hour in





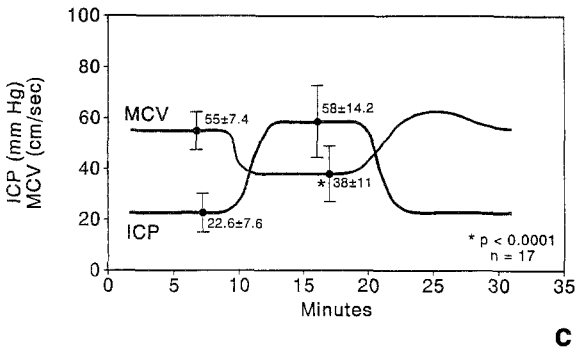


Fig. 2. (a) Illustration of a typical recording during Lundberg A waves, or plateau waves. There was always a decrease in the MCA velocity during the peak of the wave. (b) Illustration of typical changes in pulsatility of the MCA velocity signal during an A wave. Note the marked decrease in diastolic velocity during the peak of the wave, as well as the marked increase in the ICP pulse wave amplitude. (c) During a total of 17 A waves the average ICP increased from 22.6 ± 7.7 to 58 ± 14.2 mmHg, and the average MCA velocity decreased from 55 ± 7.4 to 38 ± 11 cm/sec ($p < 0.0001$). *ABP* arterial blood pressure, *MCV* middle cerebral velocity, *ICP* intracranial pressure, *EtCO₂* end tidal CO_2

duration. A complete analysis of these recordings has been previously published [41]. MCA velocity always fluctuated synchronously with the ICP B waves (see Fig. 3).

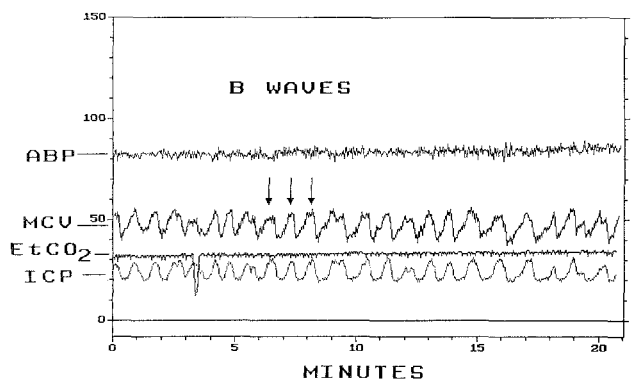


Fig. 3. Illustration of a typical recording during ICP B waves indicating simultaneous fluctuations in velocity in the MCA and intracranial pressure. The MCA velocity increases during the peak of the B waves in contrast to the decrease in MCA velocity seen during the peak of the A waves. (Note: these waves are independent of any changes in arterial blood pressure or end tidal CO_2). *ABP* Arterial blood pressure, *MCV* middle cerebral velocity, *ICP* intracranial pressure, *EtCO₂* end tidal CO_2

CO_2 Testing

Middle cerebral artery velocity response to hyperventilation was tested on 143 occasions in 20 patients. Figure 4 a shows a typical normal response to hyperventilation and decreased CO_2 concentration, and Fig. 4 b shows a poor response to hyperventilation, due to impaired CO_2 reactivity. The simultaneous recording of the other parameters (ABP and ICP) permitted the analysis of these factors in addition which were helpful when interpreting the data. For example a few patients had significant changes in their CPP during the test due to a change in blood pressure. In certain instances, with impaired autoregulation, changes in blood pressure could yield a false CO_2 response. If there was a blood pressure change greater than 10 mm of Hg during the hyperventilation test, these values were not considered valid. Values for CO_2 reactivity in this group of patients were expressed in % change in velocity/mm $EtCO_2$. The results obtained showed reactivities between 0 and 4.63% change/mm Hg for all individual hemispheres tested. The results of CO_2 reactivity within 48 hours of admission was analyzed in 15 patients. Table 2 shows the physiologic values obtained during the hyperventilation testing in these patients. The reactivity for both hemispheres was combined, and the group average was found to be

Table 2. *Physiological Values During CO_2 Reactivity and Autoregulation Testing in Patients Tested within 48 Hours of Admission*

	Before average	Range	After average	Range
CO_2 reactivity testing				
End tidal CO_2 values before and after hyperventilation (mm Hg)	33 ± 6.7	20–49	22 ± 5	13–26
MCA velocity values (cm/sec)	56 ± 19.2	30–100	44 ± 14.9	30–81
CO_2 reactivity		1.95 ± 0.77%		
Autoregulation testing				
Arterial blood pressure before and after leg cuff deflation (mm Hg)	85 ± 11.4	69–113	67 ± 11.5	47–86
		average		range
Extent of blood pressure drop (mm Hg) ± standard deviation		18 ± 7.6		9–33

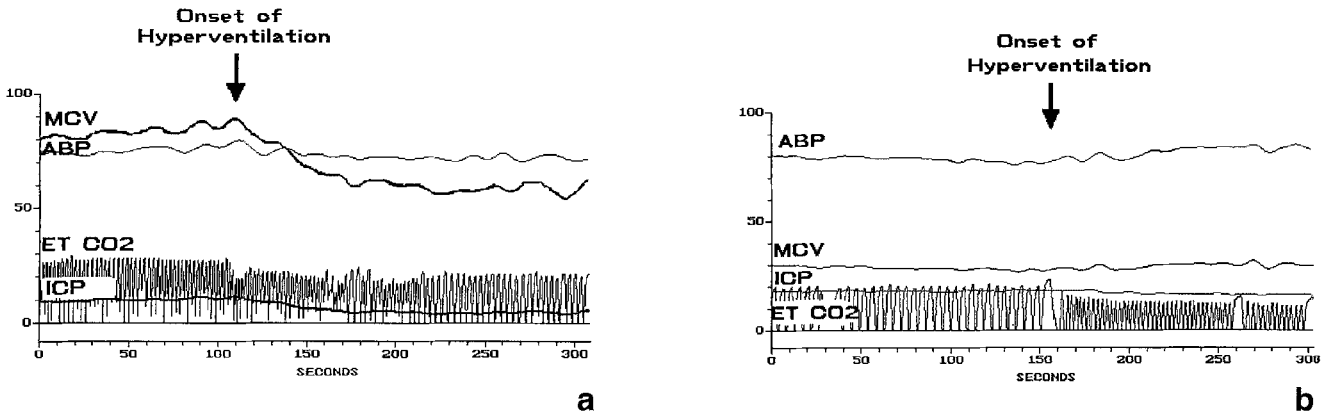


Fig. 4. (a) Illustration of a typical normal response of the MCA velocity and ICP to hyperventilation showing intact CO_2 reactivity in a head injured patient. (b) Illustration of a test indicating an absent response of the MCA velocity and ICP to hyperventilation indicating no CO_2 reactivity in another head injured patient. *ABP* arterial blood pressure, *MCV* middle cerebral velocity, *ICP* intracranial pressure, *$EtCO_2$* end tidal CO_2

1.95 ± 77%/mmHg (range 1.21–3.96). CO_2 reactivity was composed to Glasgow outcome score at 1 month and was found to be higher in patients who made a good recovery or had a moderate disability versus those who died, were severely disabled, or were in a persistent vegetative state but the difference was not statistically significant (see Table 3).

Autoregulation

The rate of regulation, which was calculated from the change in cerebrovascular resistance induced by sudden transient decreases in blood pressure, varied from 0 to 29.4 in the 118 separate studies performed on individual hemispheres (normal value = 20 ± 3 [4]). The RoR values were calculated for both hemispheres and averaged for 15 patients who were tested within 48 hours of admission (physiologic values shown in Table 2). The mean value was 6.25 ± 4.0 (range 0–13.2). The results indicated that in this group of patients the autoregulation response was not either absent or present but could be impaired to varying degrees. In patients who were serially tested, the effectiveness of the response, in many cases showed improvement over time. Figure 5 illustrates intact and absent autoregulatory responses measured by RoR in 2 head injured patients. In two patients one with intact and one with severely impaired autoregulation the RoR, also correlated to the effectiveness of the autoregulation evaluated by responses in blood flow velocity during significant spontaneous changes in blood pressure (see Fig. 5).

Following the removal of a large subdural hematoma in one patient, the postoperative CT scan demonstrated mild low density changes, characteristic of ischemic injury, in the affected hemisphere. The autoregulatory response was completely absent in the corresponding MCA territory, despite a CPP in the range where autoregulation should function (50–150 mmHg), and intact on the unaffected side. These findings sug-

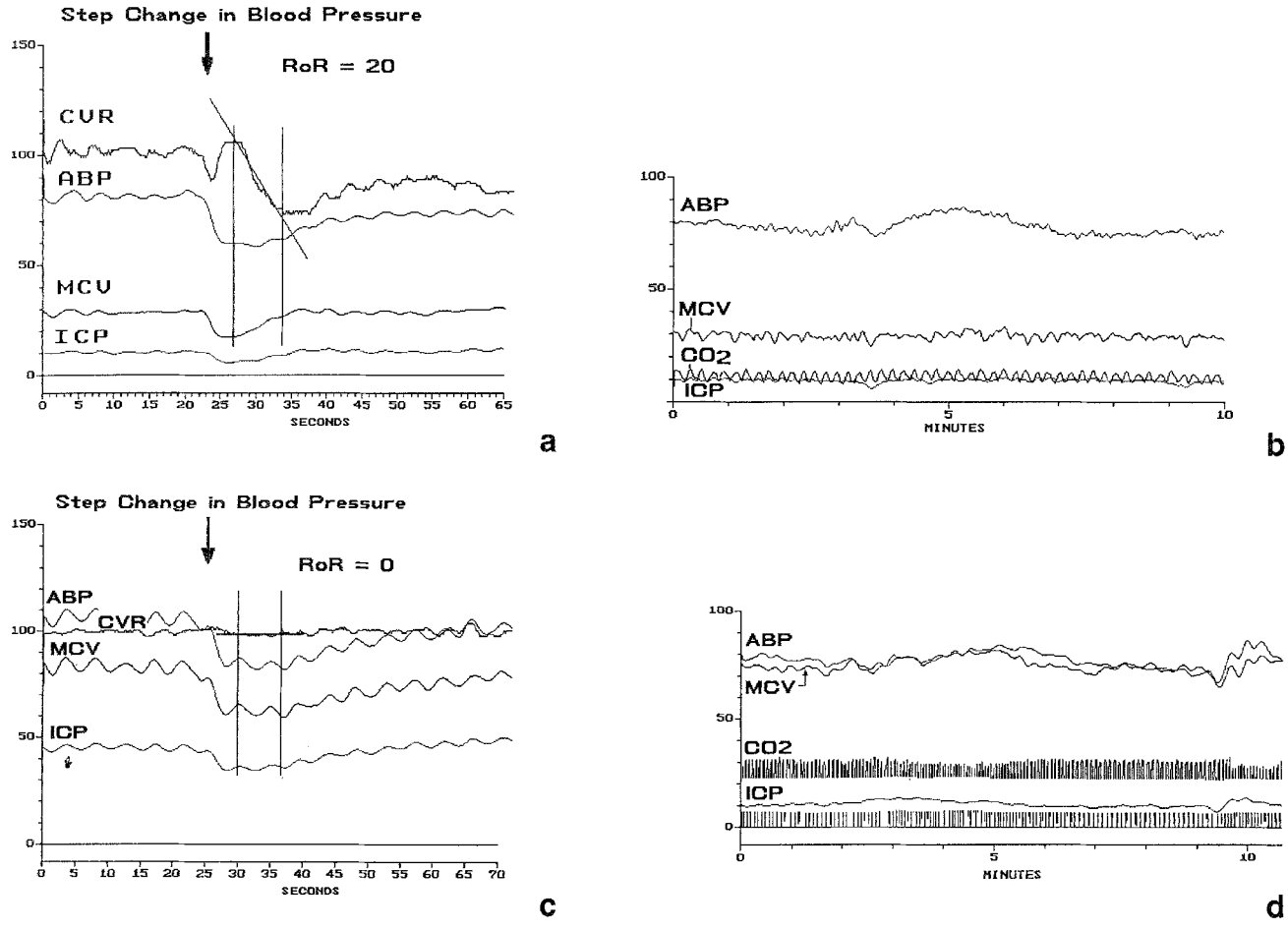


Fig. 5. (a) Illustration of an intact dynamic autoregulatory response in a patient after head injury indicated by a RoR of 20. Note that the MCA velocity has returned to baseline within 10 seconds of the step change in blood pressure. (b) Illustration of a spontaneous blood pressure change in the same patient over a longer time period with no change in the MCA velocity indicating intact autoregulation. (c) Illustration of absent dynamic autoregulation indicated by an RoR of 0. Note that the middle cerebral velocity follows the arterial blood pressure passively after the step change in blood pressure, and there is no change in the calculated cerebrovascular resistance. (d) Impaired autoregulation to a spontaneous blood pressure change illustrating passive change in middle cerebral velocity caused by fluctuations in the arterial blood pressure. *ABP* arterial blood pressure, *MCV* middle cerebral velocity, *ICP* intracranial pressure, *RoR* rate of regulation

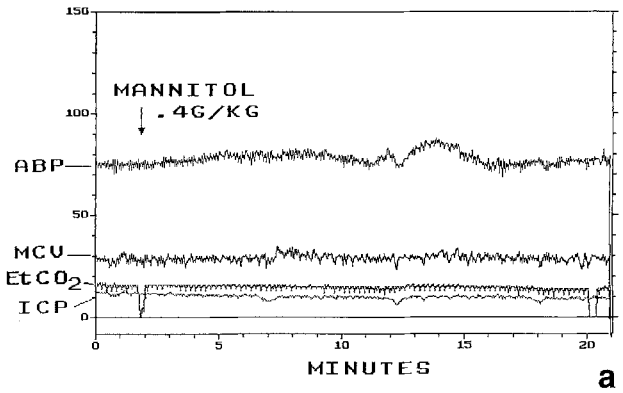
Table 3. *Comparison of Outcome to CO_2 Reactivity and Autoregulation Tested within 48 Hours of Admission*

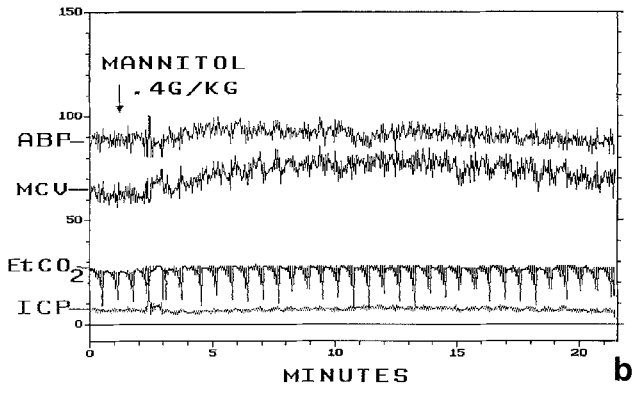
	CO_2 reactivity (% change/mm Hg)	Autoregulation (rate of regulation)
Good recovery, moderate disability (1 month)	2.25 ± 0.87 (SD) n = 9	6.0 + 4.1 (SD) n = 9
Severe disability, persistant vegetative state, dead (1 month)	1.51 ± 0.25 (SD)[a] n = 6	6.7 + 4.37 (SD)[b] n = 6

[a] $0.1 > p > 0.05$.
[b] p = not significant.

gest that a period of ischemia caused by brain compression may have been responsible for an impairment of the response.

In a patient with marked ICP elevation which resulted in reduction of the CPP below the level where autoregulation is normally functional, the autoregulatory response was completely abolished. It was also noted in one patient that an increase in CO_2 concentration during weaning from the ventilator after improvement in clinical condition was associated with a markedly impaired autoregulatory response. We compared the combined RoR for both hemispheres obtained within 48 hours of admission, to Glasgow outcome score at 1 month in 15 patients.





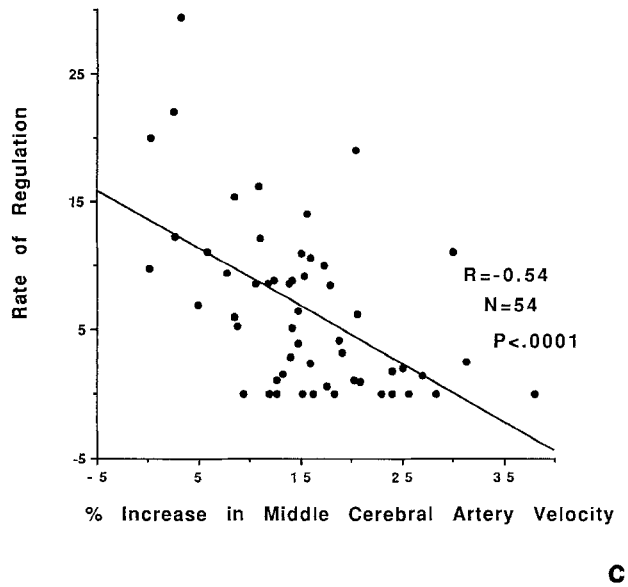


Fig. 6. (a) Illustration of the response to mannitol infusion in a patient with intact autoregulation. Note the absence of any change in MCA velocity and slight fall in ICP. (b) Illustration of the response to mannitol infusion with impaired autoregulation. Note the rapid increase in MCA velocity and little change in ICP. (c) Graph illustrating the relationship between change in MCA velocity and rate of regulation 10 minutes after an infusion of 0.4 g per kg body weight of mannitol given as a 20% solution. *ABP* arterial blood pressure, *MCV* middle cerebral velocity, *ICP* intracranial pressure, $EtCO_2$ end tidal CO_2, *G/KG* grams per kilogram

There was no correlation between the autoregulatory function and outcome in this group (see Table 3).

Mannitol Response

Following mannitol infusion of 0.4 g/kg of 20% mannitol, all patients had an increase in middle cerebral artery velocity although in certain patients the increase was very small. The greatest increase occurred approximately ten minutes following the end of the infusion. Fifty-four infusion tests were performed on 15 patients where the RoR was calculated. The physiological values for the mannitol infusion testing are shown in Table 4. The percentage increase in MCV following the infusion test was 15.4 ± 7.9 (range 0.04–38.0%). The average RoR for this subgroup was 6.7 ± 6.6. Linear regression analysis showed an inverse correlation between the RoR and the percentage increase in MCV following mannitol infusion ($r = -0.54$) ($p < 0.0001$) (see Fig. 6).

These results indicated that the increase in MCA velocity following mannitol infusion was greatest in those patients with the most impaired autoregulation and least in patients with intact autoregulation. The number of patients with completely intact autoregulation, however, was small. There was no correlation by linear regression analysis between the RoR or the increase in MCV and the percent decrease in ICP.

Table 4. *Physiologic Values Before and After Mannitol Infusion Testing*

	Before	After
Arterial blood pressure (mm Hg)	88 ± 12	91 ± 13
Cerebral perfusion pressure (mm Hg)	71 ± 11	76 ± 12
Intracranial pressure (mm Hg)	17 ± 12	15 ± 10
MCA velocity (cm/sec)	61 ± 23	70 ± 28

± Standard deviation.

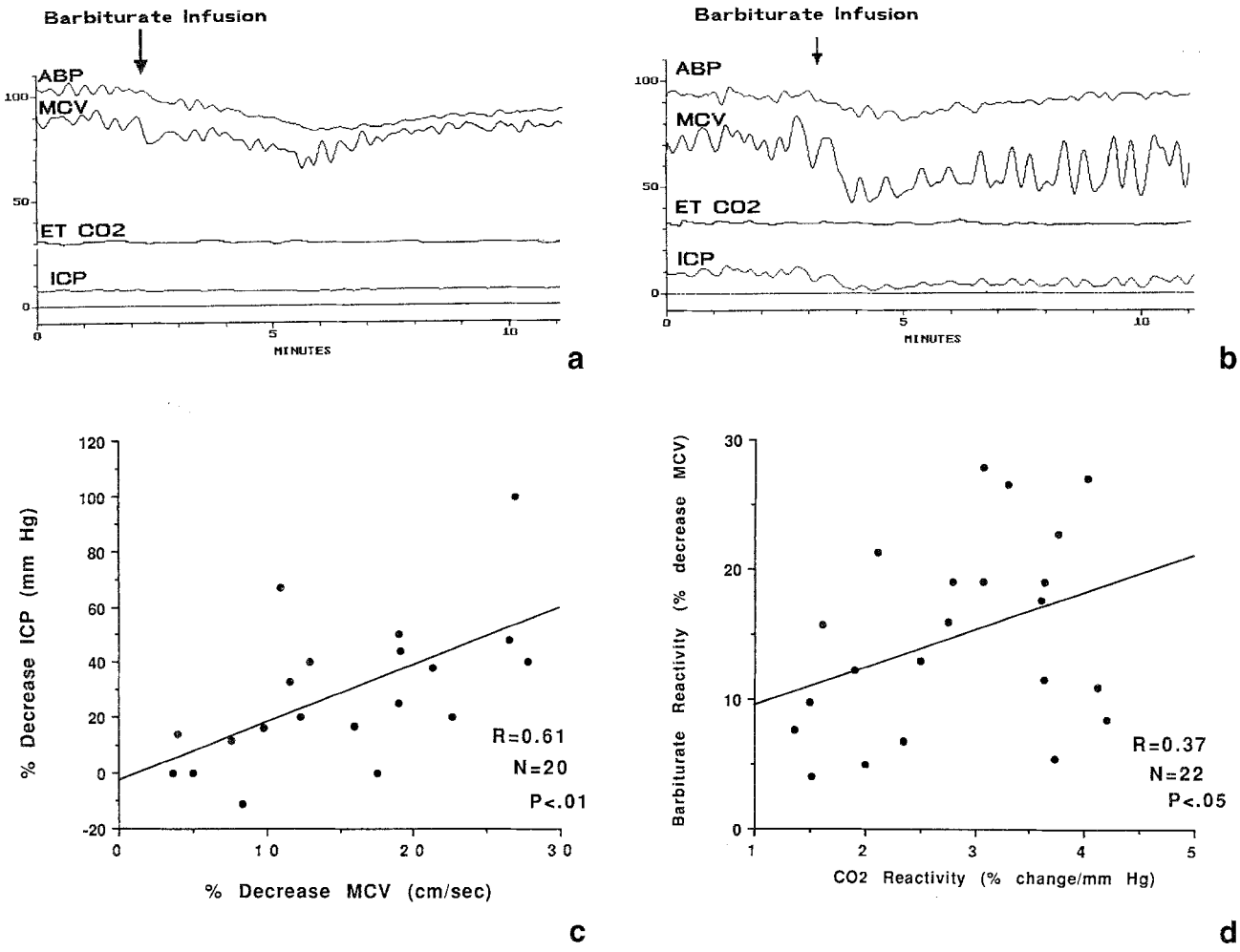


Fig. 7. (a) Optimal response to barbiturate infusion indicated by a marked decrease in MCA velocity and intracranial pressure with a minimal change in arterial blood pressure and an improvement in cerebral perfusion pressure. (b) Poor response to barbiturate infusion indicated by a slight decrease in the blood pressure and a small decrease in the middle cerebral velocity but no change in the intracranial pressure and a reduction in cerebral perfusion pressure. (c) Response to barbiturate test. This graph illustrates the comparison between the percent decrease in middle cerebral artery velocity and the percent decrease in intracranial pressure induced by a thiopentone infusion of 5 mg per kg body weight. (d) This graph illustrates the relationship between CO_2 reactivity and barbiturate reactivity as measured by MCA velocity change indicating a significant relationship between the two parameters. *ABP* arterial blood pressure, *MCV* middle cerebral velocity, *ICP* intracranial pressure, *$EtCO_2$* end tidal CO_2

Barbiturate Response

Following barbiturate administration the typical response which was seen was a small transient decrease in blood pressure followed by a return to pre-infusion or near pre-infusion values in some patients, and a more persistent blood pressure decrease in others. There was a decrease in MCA velocity during all of the tests performed. The average decrease in MCA velocity was 15.1 ± 7.6% (range 3.7–27.8%). The cerebral perfusion pressure increased on 3 occasions and decreased on 17 (average change –5.9 mm/Hg ± 5.3). The ICP increased slightly on one occasion and decreased or was unchanged in the remaining 19 tests (average decrease 2.65 mm/Hg ± 2.5), however, the ICP before the test was not elevated significantly in all patients (average 10.9 mm/Hg ± 7.3, range 3–25). Patients considered to have a more favorable response to barbiturates had a decreased blood flow velocity and a decreased ICP, without a significant decrease, or in some cases an improvement, in perfusion pressure. Patients considered to have an unfavorable response had either a minimal change in blood flow velocity and ICP or a significant decrease in cerebral perfusion pressure (Fig. 7). Linear regression analysis demonstrated a significant correlation be-

tween the decrease in MCA velocity and the percentage decrease in ICP induced by the test dose of barbiturates ($r = 0.61$, $n = 20$, $p < 0.01$) (see Fig. 7 c). There was also a significant relationship, demonstrated by linear regression analysis, between the CO_2 reactivity and the MCA velocity change in response to barbiturate infusion ($r = 0.37$, $n = 20$, $p < 0.05$) (see Fig. 7 d).

Discussion

Theoretical Considerations

The evaluation of CBF, and changes in CBF following head injury have important potential clinical and research applications. Some of the abnormalities in CBF which have been identified following head injury include impaired autoregulation [19, 39, 47], altered CO_2 reactivity [14, 15, 19, 20], increased CBF (hyperemia) [46], decreased CBF due to a variety of causes including low cerebral metabolism, high ICP, and vasospasm [16, 19, 20, 26, 42, 50]. Various methods to evaluate CBF available for clinical use include 133-xenon clearance using portable detectors [20, 46, 50] xenon CT [13], single photon emission computerized tomography [9] (SPECT). These methods provide static flow measurements with relatively good spatial resolution, but cannot provide continuous flow data. Continuous flow measurement techniques include thermal dilution probes [25] and laser Doppler probes [22] which can measure focal cortical perfusion in a selected area, and must be implanted surgically. In order to provide continuous flow information to larger brain regions, techniques which evaluate arterial inflow or venous outflow such as an electromagnetic flowmeter have been used, mainly for research purposes [43]. When using a technique to measure arterial inflow through a single vessel to reflect more generalized CBF, or CBF changes, one makes the additional assumption that the perfusion territory of the particular vessel remains constant under various manipulations.

Continuous transcranial Doppler monitoring can also now be used to non-invasively monitor relative changes in CBF, by measuring relative blood flow velocity changes through the inflow vessels, under certain specific circumstances [4, 5, 8, 29, 32, 33, 55].

In order to accomplish this, certain conditions must exist:

1. The Doppler probe must be fixed in place to record from the same sample volume and a constant angle of insonation must be maintained, preferably on a straight portion of the artery.

2. There should be a good signal to noise ratio, and minimal vascular branching or turbulence in order not to disrupt the laminar flow.

3. The arterial diameter at the recording site must not change either unpredictably or to the extent that it introduces a significant change in velocity which is not due to a change in flow during the interval measured.

4. The perfusion territory of the artery must not change, during the interval studied, to the extent that flow changes observed reflects changes in perfusion territory rather than changes in blood flow to a defined area of brain.

To gain an index of relative blood flow, the preferred method is to record the velocity value of the outline of the sepctral signal (V_{max}) produced by the TCD which corresponds to the flow velocity at the center of the artery [5, 29, 43]. When this value is averaged over a given time interval it is referred to as the time averaged mean velocity.

Very strong correlations between changes in volume flow in the carotid artery and changes velocity or V_{max} in the middle cerebral artery have been demonstrated in humans, by Lindegaard *et al.* [29]. These investigators observed spontaneous blood flow changes during carotid endarterectomy while simultaneously recording MCV using Doppler ultrasound and carotid blood flow using an electromagnetic flowmeter. Since flow through a vessel is the product of velocity and cross sectional area of the vessel, these results indicate that under these circumstances basal artery diameter must not vary to any significant degree because the majority of the velocity changes are directly reflecting changes in flow.

To measure the effectiveness of autoregulation or CO_2 responsiveness in patients, knowledge of the absolute blood flow is not necessary. More valuable is a continuous measure of relative changes in blood flow under changing conditions of ICP, ABP, or CO_2. By observing these changes, reactivity can be calculated much more easily than with more cumbersome non-continuous blood flow methods.

The correlation between flow and velocity in response to a limited number of drugs has also been tested. Nitroglycerin appears to induce large vessel vasodilatation thereby making velocity not a useful index of flow in response to this drug [55]. Animal experiments using dogs indicate that velocity and CBF respond equally in response to the administration of the anesthetic agent sufentanil [57]. A recent animal study has also indicated that basal vessel

velocity and CBF are influenced similarly by increased ICP [11].

A Waves and B Waves

The finding of a decrease in MCA velocity, reflecting reduced CBF, during ICP A waves is consistent with previous observations by Lundberg *et al.* [31], who measured CBF during and after an A wave in a patient and found a marked decrease in CBF during the peak of the wave. Risberg *et al.* [49], demonstrated an increase in cerebral blood volume during A waves using a radioisotope measurement technique. It has been hypothesized that A waves occur when a positive feedback cycle is established in states of reduced intracranial compliance [45, 51]. Under these circumstances the increased cerebral blood volume associated with vasodilation results in marked increases in ICP, which results in a decrease in cerebral perfusion pressure which causes a reduction in CBF. Our results are consistent with this hypothesis and in addition, illustrate the dynamics of the ICP, CBF relationship. In contrast to A waves, ICP B waves usually demonstrate an *in phase* relationship to simultaneous fluctuations in the MCA velocity. These observations support the hypothesis that B waves are the result of vasomotor waves of the small regulating cerebral arteries [10] which normally produce CBF changes indicated by the MCA velocity and cerebral blood volume changes reflected in the ICP. Hashimoto *et al.* [22] have recorded ICP, MCA velocity with TCD, and cortical flow using laser Doppler during ICP B waves and found synchronous *in phase* fluctuations of all 3 parameters, supporting the concept that MCA velocity changes are primarily reflecting CBF changes during B waves.

Our observations indicate that there appear to be 2 different patterns of CBF responses associated with intermittent cerebral vascular dilatation:

1) ICP increases associated with vasolidilatation and flow *increases* as seen with B waves;

2) ICP increases associated with vasodilatation and flow *decreases* as seen with A waves.

The precise reasons for the different responses are not entirely clear but it is likely that differences in the intracranial compliance, as well as the anatomic location and extent of the vasodilatation, play a major role in determining which response will take place.

CO_2 Reactivity

Measurement of CO_2 response using TCD is based on the observations that the basal artery diameters remain relatively constant during CO_2 changes [21, 23], therefore changes in basal artery velocity are directly proportional to changes in blood flow caused by the more distally located regulating arteries [12, 55]. The measurement of CO_2 reactivity following head injury may be valuable in estimating prognosis, and also predicting the effectiveness of hyperventilation for ICP control. Impairment of the normal blood flow response to CO_2 changes in head injured patients has been reported in the past, and poor CO_2 reactivity measured both by TCD and the xenon flow method has also been associated with a poor prognosis following head injury [15, 19, 52]. Our results indicate that the CO_2 reactivity for the group measured within 48 hours of admission (1.95%/mmHg) was slightly reduced compared to published normal values (3%/mm Hg) [38]. The present results indicate a higher CO_2 reactivity in those patients with a better outcome, however, the results did not reach statistical significance, mainly due to the small sample size.

The role of hyperventilation treatment following head injury is controversial. Recent experimental evidence suggests that the reductions in cerebral blood volume and ICP reductions following hyperventilation are transient [40] and therefore this form of ICP control may be better suited for situations where shorter periods of ICP control are needed. Nevertheless, if hyperventilation is to be considered for ICP control, calculation of the degree of CO_2 reactivity using TCD in individual patients may be useful.

Autoregulation

Studies of autoregulation in head injured patients have been performed in the past by inducing a step change in ABP and measuring the CBF before and after the ABP change using the Xenon flow method [19, 39, 47]. An alternative to this methodology was introduced by Aaslid *et al.* [4] which employs TCD monitoring to evaluate *dynamic* autoregulation in humans. The validity of this method of assessment of autoregulation has been questioned on the grounds that other factors such as conducting vessel diameter changes or compliance effects of the cerebrovascular bed may cause changes in velocity which are not the result of autoregulation [24]. A recent experimental study which measured MCA flow changes during autoregulation, using an ultrasound flow index, indicate that the TCD method is indeed a valid way to assess cerebral autoregulation [5]. In the same study, comparisons of arterial inflow velocity to venous out-

flow velocity recordings during transient blood pressure decreases, show similar responses in the two parameters, and support the validity of the TCD method [5]. A subsequent study which directly compared electromagnetically measured flow and velocity, measured using TCD, during autoregulation in humans, confirms the validity of the TCD method [43].

Within this subgroup of patients with head injury (most were severe) there was no correlation between the admission GCS or the Glasgow outcome score and the RoR. Previous studies on autoregulation following head injury have also indicated that the autoregulatory response can be impaired in patients who make a good recovery or who are in good clinical condition [19]. Our experience in this group of patients indicated that several factors other than the severity of the brain injury may influence the effectiveness of the autoregulatory response. We identified 3 factors which led to reduced autoregulation. These factors have been shown experimentally to impair autoregulation and include:

1) direct impairment to the autoregulatory mechanism, induced by trauma or ischemia [28, 36];

2) low cerebral perfusion pressure [27], due to low ABP and/or high ICP at the time of testing;

3) recent increase in CO_2 concentration [4].

These observations illustrate the fact that the autoregulatory response may be sensitive to a variety of factors which should be considered during the testing, and also for optimal patient management. Manipulation of certain factors such as CPP or CO_2 concentration may be effective strategies to improve the autoregulatory response in individual patients and therefore may have potential implications in their care. Moreover, further study of autoregulation in head injured patients using this simplified methodology may provide more information about the causes of impairment of autoregulation and provide a method to evaluate strategies to improve this response.

Mannitol Response

A potentially important effect of mannitol on ICP reduction may be mediated by cerebral vasoconstriction, which in turn can decrease cerebral blood volume. Mannitol can improve the rheologic properties of blood which in turn induces a vasoconstriction to maintain the same blood flow, provided the autoregulation is intact. Experiments in animals [37] and measurements of physiological responses in humans [39] support this hypothesis. In patients with poor or absent autoregulation, CBF can be increased immediately following mannitol administration due to the lack of vasoconstriction [22, 34, 39].

We found a consistent increase in MCA velocity following mannitol infusion in our patients with impaired autoregulation, and usually very small increases when autoregulation was intact. This is indicated by the inverse correlation between the RoR and the percentage increase in MCA velocity, 10 minutes after infusion. It is likely that the changes in MCA velocity following mannitol infusion were due primarily to changes in CBF, however, we are aware of only one study comparing relative increases in CBF and MCA velocity following mannitol infusion in humans. This study demonstrated similar changes in MCA velocity and cortical flow using laser Doppler in patients with subarachnoid hemorrhage, suggesting that changes in MCA velocity are primarily reflecting changes in flow [22]. We did not find an inverse relationship between the percent increase in velocity and percent decrease in ICP, similar to the relationship found between CBF change and ICP reduction after mannitol infusion found by Muizelaar *et al.* [39]. This lack of correlation may be explained by the fact that we were not able to obtain data from both hemispheres as Muizelaar *et al.* [39] did, and a smaller dose of mannitol was used in our study.

Barbiturate Response

One of the major actions of barbiturates on cerebral function is believed to result from their ability to inhibit synaptic transmission between neurons, therefore reducing metabolic demand [48, 54]. In the presence of intact metabolism and blood flow coupling, barbiturates can reduce cerebral blood flow and cerebral blood volume, by vasoconstriction, inducing a decrease in ICP [14, 44]. Under normal circumstances in non brain injured patients, barbiturates are very effective in reducing ICP. In patients with head injury several abnormalities can exist which would make barbiturates much less effective in reducing ICP. One condition is already severely reduced cerebral metabolism or cerebral metabolic rate of oxygen consumption ($CMRO_2$) which appears to have a relationship to the severity of injury [50]. Another abnormality is poor metabolic/CBF coupling. It has been demonstrated using xenon CBF studies, that the relative reduction in CBF induced by barbiturates can

help to predict the effectiveness of these agents to reduce ICP in individual patients [14, 44].

Head injured patients may vary greatly in their potential to benefit from barbiturates for ICP control [14, 18, 44,]. Previous studies have failed to show an overall benefit of barbiturates following head injury [18, 56], however, Eisenberg *et al.* [18] identified a subgroup of patients which responded more effectively, with better ICP control. This subgroup appeared to benefit from the therapy.

Using TCD monitoring to evaluate the CBF response of individual patients to barbiturate therapy may provide an alternative to the xenon CBF method and provide similar information in the clinical setting. Our results indicate, similar to those results obtained using the xenon method [44] that the relative reduction in MCA velocity was highly correlated with the relative reduction in ICP following the barbiturate infusion. In addition our finding of a significant relationship between the CO_2 reactivity and the relative MCA change following barbiturate infusion is consistent with previous results using the xenon CBF method [14]. The potential exists to use TCD to evaluate the hemodynamic responses to a test dose of barbiturates and selected patients for therapy based on the response.

Conclusions

Monitoring of MCA velocity in the intensive care setting can offer insights into hemodynamic alterations in patients suffering from head injuries. Due to technical considerations including probe fixation and patient movement it appears to be most feasible to perform TCD monitoring for short time periods, during which trained personnel can assure proper continuous signal consistency. Autoregulation and CO_2 reactivity as well as reactivity to barbiturates and mannitol can be tested non-invasively and may offer useful information in individual patients requiring ICP control. The ability to test autoregulation using a non-invasive and easily repeatable test may be useful to identify individual patients with significant impairment of autoregulation in order to take extra measures to protect them against extreme changes in cerebral perfusion pressure which may be harmful. It also may have applications for future research into the nature of the mechanisms responsible for the impairment of this response following head injury. The recent development of 2 channel Doppler will allow for simultaneous recording from both MCAs while performing the testing described.

Acknowledgement

This work was supported by the William P. Van Wagenen Fellowship awarded by the American Association of Neurological Surgeons (DWN).

This work was also supported by Clinical Investigator Development Award 1K08 NS 015969 01, and NIH 1 P50 NS 30305-01 (DWN).

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Comments

The authors used prolonged transcranial Doppler monitoring in head injured patients. Correlation with ICP fluctuations allowed identification of A and B waves. During the monitoring sessions CO_2 reactivity and dynamic autoregulation were also evaluated. In addition the hemodynamic response to test treatment with mannitol and barbiturates was studied. The results confirmed that CO_2 reactivity and autoregulation are variably disturbed in head injured patients. In the actual study, correlation between disturbed cerebral vaso-reactivity and outcome was marginal at best, which suggests that disturbance of these indices is probably not related to secondary brain damage but rather a variable sequence of the primary injury. The concept of studying the hemodynamic response to a test dose of the principal medications for ICP, mannitol and barbiturates, is interesting although the results do not provide any new pathophysiological insights. For future application of this method, however, barbiturate application should be adjusted according to the EEG response. It appears quite possible that in the present series in some patients with an apparently poor barbiturate response no sufficient EEG suppression was obtained.

H. Steiger

This is an important and very interesting manuscript from one of the most reknowned groups in transcranial Doppler monitoring. Using continuous transcranial Doppler monitoring the authors evaluate autoregulation in patients with severe head injury. Moreover, the effect of therapeutic approaches, hyperventilation, mannitol infusion and barbiturates on ICP, CPP, and CBF, as monitored by MCA velocity, is described and related to the degree of impaired autoregulation. This approach sets the path for the future where, based on such testing of various therapeutic approaches in individual patients, decisions can be made as to which therapeutic approach is most appropriate in individual cases. I have some concern, however, as to relative risks of performing the tests of autoregulation and CO_2 reactivity. End tidal CO_2 values of below 20 mmHg as the authors describe during many reactivity tests (Table 2) certainly carry the risk of severe reduction of CBF and ischemic brain damage. The low mean blood pressure during autoregulation testing, sometimes down to a level below 50 mmHg, although of short duration, is inappropriate and may be dangerous.

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