Doppler CO₂ Test as an Indicator of Cerebral Vasoreactivity and Prognosis in Severe Intracranial Hemorrhages

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Background and Purpose: Transcranial Doppler ultrasonography is a noninvasive, reproducible technique that allows the assessment of CO₂-induced cerebral vasomotor reactivity. We investigated the effect of CO₂ changes on cerebral blood flow velocity in patients with severe intracranial hemorrhage and evaluated the relation between CO₂ reactivity, intracranial pressure, and outcome.

Methods: Transcranial Doppler parameters, intracranial pressure, arterial blood pressure, and Paco₂ were measured simultaneously in 40 patients. To determine CO₂ reactivity, the initial Paco₂ of each patient was lowered by at least 6 mm Hg by controlled hyperventilation. Relative CO₂ reactivity was defined as the percent change in mean flow velocity per mm Hg Paco₂ (averaged during 20 heart cycles before and after approximately 15 minutes of increased hyperventilation).

Results: A significantly reduced relative CO₂ reactivity was observed in the patient group compared with a healthy, age-matched control group. Relative CO₂ reactivity was maintained significantly better in patients with moderate intracranial pressure than in patients with markedly increased intracranial pressure. An indirect correlation was found between intracranial pressure and relative CO₂ reactivity (r = -0.89; p < 0.001). Clinical outcome was significantly related to the initial relative CO₂ reactivity.

Conclusions: Transcranial Doppler CO₂ testing in patients with severe cerebral disease and elevated intracranial pressure provides useful information regarding hemodynamic state, prognosis, and determination of beneficial effects of specific therapy.

KEY WORDS • carbon dioxide • cerebral hemorrhage • stroke outcome • ultrasonics

Controlled hyperventilation is part of intensive-care management, in addition to barbiturate therapy and administration of osmotic agents, to reduce elevated intracranial pressure (ICP) caused by decreasing cerebral blood flow in intact (vasoactive) areas and to improve cerebral blood flow in the most damaged (vasoparalytic) brain areas (the inverse steal phenomenon). Only in this case does reduction of Paco₂ (resulting in an increase in local perivascular pH) cause a vasoconstriction of cerebral resistance vessels and a concomitant decrease of cerebral blood volume and ICP. Because the efficiency of barbiturate and mannitol administration in reducing ICP also depends on preserved cerebral CO₂ reactivity and the use of these substances may have relevant side effects, information on the cerebrovascular response to changes in Paco₂ may serve as a prognostic marker and a guide to rational therapy.

Methods for detection of the cerebrovascular response to CO₂ changes have included angiography, regional cerebral blood flow techniques, and positron emission tomography. However, compared with these techniques, the development of transcranial Doppler ultrasonography (TCD) provides a noninvasive, nonradioactive, and less expensive method to assess the cerebrovascular response to CO₂ changes in connection with a time resolution detecting blood flow velocity changes in the range of seconds. We designed the present study to determine the effect of CO₂ changes on cerebral blood flow velocity in intensive-care-unit patients with severe intracranial hemorrhage. To our knowledge, this has been carried out for the first time in such a group of patients. The relations between CO₂ reactivity, ICP, and clinical outcome were evaluated.

Subjects and Methods

Forty patients (25 males and 15 females) with traumatic subarachnoid hemorrhage, intracerebral hemorrhage resulting from cerebral contusion, and spontaneous intracerebral hemorrhage (Table 1) were studied. The initial management of all patients included controlled ventilation with continuous moderate hyperventilation (Paco₂ approximately 32–36 mm Hg) and computed tomographic scanning, which was performed in all patients during the first 24 hours after hospital
admission and repeated when clinically indicated. The control group consisted of 20 healthy age-matched subjects (12 males and 8 females) (Table 1). In 24 patients, barbiturate coma was induced by intravenous infusion of 5-11 mg/kg and continued with infusion of 4-8 mg/kg per hour to achieve a burst-suppression pattern on the electroencephalogram. Furthermore, conventional therapy for the individual underlying brain damage, such as corticosteroid treatment, application of osmotic agents, control of blood pressure, and infusion of adequate amounts of crystalline and colloid fluids, was applied. In all patients, ICP was measured with an epidural device (Galetic Ltd., Dunvegan, Isle of Skye, Scotland). Arterial blood pressure was measured with a radial pressure transducer, and $\text{Paco}_2$, $\text{Pao}_2$, and pH were monitored by blood gas analysis. End-tidal $\text{CO}_2$ concentration was monitored in all patients using the respirator. In all patients, the extracranial vascular status was additionally determined with a directional continuous-wave Doppler device (4-MHz emitting frequency; Delalane/Dyna, Paris). Hemodynamically relevant stenosis of the extracranial and intracranial arteries supplying the brain was found in none of the patients.

Blood flow velocity of the middle cerebral artery was evaluated using an EME TC 2-64 B 2-MHz pulsed TCD device. In all cases with an asymmetrical distribution of the hemorrhage (as determined from the computed tomographic scans), the epidural pressure transducer was placed on the side with more blood, and the parameters of the ipsilateral middle cerebral artery were evaluated. If the two hemispheres were affected to a similar degree, the parameters of the middle cerebral artery were evaluated on the side of the implanted epidural device. The Doppler probe was fixed by means of a specially designed probe holder. Flow patterns of the middle cerebral artery were recorded either intermittently at least once a day or continuously during the period of increased hyperventilation.

In the patients, TCD $\text{CO}_2$ reactivity tests were performed during the first 48 hours after onset of hemorrhage. Usually, TCD $\text{CO}_2$ reactivity tests are performed by inducing hypocapnia through hyperventilation and hypercapnia through $\text{CO}_2$ inhalation. To avoid a possible increase of ICP in our patients, however, inhalation of $\text{CO}_2$ (or reduction in ventilation) was not used in any patient. To evaluate $\text{CO}_2$ reactivity, the initial $\text{Paco}_2$ (32-36 mm Hg) of each patient was therefore lowered by increased hyperventilation for at least 6 mm Hg. During this phase, the envelope curve of middle cerebral artery Doppler frequency spectrum, the ICP, the arterial blood pressure, and the end-tidal $\text{Paco}_2$ concentration were continuously monitored and stored on magnetic tape. The data were transferred off-line to a personal computer. In addition, the mean flow velocity was calculated from one cardiac cycle to the next using a computer-assisted integration procedure. To determine the $\text{CO}_2$ reactivity, the mean flow velocity (MFV) was averaged for 20 heart cycles before and after approximately 15 minutes of increased hyperventilation, when the flow velocity remained stable again. Relative $\text{CO}_2$ reactivity was defined as the ratio of percent decrease in averaged MFV and the difference between $\text{Paco}_2$ measurements before and after approximately 15 minutes (the end-tidal $\text{CO}_2$ concentration has to remain stable) of increased hyperventilation (percent change in averaged MFV per mm Hg $\text{Paco}_2=\%\Delta\text{MFV}/$ mm Hg $\text{Paco}_2$). There was no change in medication during the $\text{CO}_2$ reactivity test. The $\text{CO}_2$ reactivity of the controls was determined proceeding from a slight hyperventilation (end-expiratory $\text{CO}_2$ between 33 and 37 mm Hg) to reach a comparable $\text{Paco}_2$, initial value in the patient and control groups.

The patients were classified into four groups (A-D) on the basis of the averaged ICP values during the last hours before increased hyperventilation: group A, ICP <15 mm Hg (n=9); group B, ICP 15-25 mm Hg (n=13); group C, ICP 25-35 mm Hg (n=9); and group D, ICP 35 mm Hg (n=9). The Glasgow Outcome Scale score was assigned to each patient at 3 months postinjury. The scale comprises the following five categories: died within 3 months (DEAD), persistent vegetative state (PVS), severe disability (SD), moderate disability (MD), and good recovery (GR). For purposes of statistical analysis, the DEAD and PVS categories were combined because the sample comprised only two PVS patients. The outcome ratings were made independently by two observers, one without any knowledge of the TCD findings.

All values are specified as mean±SD. A one-way analysis of variance (ANOVA) was used for overall intergroup comparisons (e.g., $\text{CO}_2$ reactivity in groups A-D). Subsidiary intergroup comparisons (e.g., $\text{CO}_2$ reactivity between groups A and B) were made with the unpaired t test corrected for multiple comparisons using Bonferroni's inequality. Intragroup comparisons (e.g., ICP in group A before and after increased hyperventilation) were evaluated using Student's t test for paired data. Regression analysis was performed using least-squares approximation. A calculated difference of $p<0.05$ was considered statistically significant.

**Results**

Comparing the basic parameters obtained in the four patient groups classified according to ICP values (group...
A, ICP <15 mm Hg; group B, ICP 15–25 mm Hg; group C, ICP 26–35 mm Hg; and group D, ICP >35 mm Hg), no significant intergroup differences were found for $P_{a CO_2}$, $P_{a O_2}$ and mean arterial blood pressure (Table 2). The increase in hyperventilation caused an equivalent significant decrease of $P_{a CO_2}$ in all groups. Simultaneously, a significant reduction of ICP could be observed in group A (31.9%), group B (31.7%), and group C (17.1%). In group D only a slight ICP decrease of 10.4% was found for a short period after increased hyperventilation (Table 2). The mean arterial blood pressure and $P_{a O_2}$ were not affected by the increase in ventilation in any group. The initial mean ($\pm SD$) PCO$_2$ of the control group was 35±3.8 mm Hg and did not differ significantly from any of the four patient groups. The mean PCO$_2$ decreased to 28±4.1 mm Hg by in-  

Values are mean±SD. No significant intergroup differences before (I) and after (II) hyperventilation for $P_{a CO_2}$, $P_{a O_2}$, MABP. Intragroup comparisons showed significant differences for $P_{a CO_2}$ before and after hyperventilation in groups A–D ($p<0.005$; paired $t$ test) and for ICP in groups A ($p<0.05$; paired $t$ test), B ($p<0.001$; paired $t$ test), and C ($p<0.05$; paired $t$ test) but not in group D. ICP, intracranial pressure; MABP, mean arterial blood pressure.

A significantly reduced mean relative CO$_2$ reactivity (2.0±1.1%ΔMFV/mm Hg $P_{a CO_2}$) was observed in all patients compared with the healthy age-matched control group (3.7±0.5%ΔMFV/mm Hg $P_{a CO_2}$; $p<0.0001$; ANOVA; Figure 1A). However, relative CO$_2$ reactivity was maintained significantly better in patients with moderately elevated ICP than in patients with clearly increased ICP ($p<0.0001$; ANOVA); whereas group A (ICP <15 mm Hg) showed a relative CO$_2$ reactivity (3.6±0.7%ΔMFV/mm Hg $P_{a CO_2}$) comparable with the control group, a continuous decrease up to 0.9±0.3%ΔMFV/mm Hg $P_{a CO_2}$ occurred in group D (ICP >35 mm Hg). Accordingly, an indirect correlation was found between ICP and the relative CO$_2$ reactivity ($p<0.001$; $r=-0.89$; Figure 1), although some patients with similar basic ICP revealed clearly different relative CO$_2$ reactivity. For example, in patients with a basic ICP between 20 and 22 mm Hg, relative reactivity could vary between 1.3 and 3.1%ΔMFV/mm Hg $P_{a CO_2}$ (Figure 2).

A one-way ANOVA showed a significant correlation between outcome and initial relative CO$_2$ reactivity ($p<0.0001$; ANOVA; Figure 2). Whereas the patients in group GR showed a largely maintained reactivity (3.4±0.7%ΔMFV/mm Hg $P_{a CO_2}$) that was not significantly different from that of the control group, a significant decrease occurred up to the patients categorized as PVS or DEAD (group PVS/DEAD, 0.8±0.3%ΔMFV/mm Hg $P_{a CO_2}$; GR versus MD, $p<0.01$; MD versus SD, $p<0.001$; SD versus PVS/DEAD, $p<0.005$). Because the difference between the GR group and the control group was not statistically significant, the three other patient groups showed a significantly reduced CO$_2$ reactivity compared with the control group. No patient of the SD group and the PVS/DEAD group exceeded a

**TABLE 2.** Comparison of Basic Parameters in Patients of Groups A (ICP <15 mm Hg), B (ICP 15–25 mm Hg), C (ICP 26–35 mm Hg), and D (ICP >35 mm Hg) Before and After Increased Hyperventilation

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<td>$P_{a CO_2}$ (mm Hg)</td>
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<td>ICP (mm Hg)</td>
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**Figure 1.** A: Bar graph showing comparison of mean relative CO$_2$ reactivity of patient group (n=40) with healthy age-matched control group (n=20). B: Scatterplot showing relation between relative CO$_2$ reactivity and ICP ($r=-0.89$, $p<0.001$). Each point represents one patient.

**Figure 2.** Plot showing relation between relative CO$_2$ reactivity and outcome according to the Glasgow Outcome Scale score assigned to each patient 3 months postinjury (GR, good recovery; MD, moderate disability; SD, severe disability; PVS/DEAD, persistent vegetative state/dead). Filled circles represent relative CO$_2$ reactivity in individual patients; white squares show mean±SD values of each group. Values of control group are drawn for comparison.
relative CO₂ reactivity of approximately half that of the control group.

Discussion

Our investigations show that a significantly reduced mean CO₂ reactivity was to be observed in the patients compared with the healthy age-matched control population. The mean CO₂ reactivity of the control group was comparable with the results of other studies using TCD or cerebral blood flow CO₂ reactivity measurements.\(^{12,13,19}\) Comparison of CO₂ reactivity with the ICP values reveals three ranges: in normal or only slightly raised ICP, a CO₂ reactivity of less than 2%ΔMFV/mm Hg PaCO₂ was not found in any case. This indicates that there was at best a slight alteration of CO₂ vasoreactivity in these patients in the initial clinical course. With an ICP between 20 and 35 mm Hg, the CO₂ reactivity varied between 1%ΔMFV/mm Hg PaCO₂ and 3%ΔMFV/mm Hg PaCO₂. The CO₂ reactivity in this ICP range may thus still be maintained relatively well initially. However, an appreciable disturbed CO₂ reactivity may also have occurred in the initial clinical course as a sign of severe cerebral damage.\(^{3,7}\) Whereas an early prognosis with regard to the further clinical course was difficult up to now in patients with these ICP values,\(^{20}\) we consider that the TCD CO₂ reactivity test may provide additional information on the state of cerebral function. In patients with ICP values higher than 35 mm Hg, the markedly reduced CO₂ reactivity (less than 1.5%ΔMFV/mm Hg PaCO₂) already indicated that CO₂ vasomotor response was largely abolished initially, reflecting very severe cerebral damage. Compared with cerebral blood flow studies,\(^{4,6}\) it is noteworthy that the CO₂ reactivity was not completely abolished in any of the patients we investigated, even in those with a highly pathological ICP. Enevoldsen and Jensen\(^{3}\) observed an abolished response to hyperventilation in four patients after a period with high ICP, numerous plateau waves, and multiple attacks of decerebrate rigidity. These results indicate that complete loss of CO₂ reactivity evidently occurs only after long periods of highly pathological ICP. Because in our study CO₂ reactivity was determined during the initial clinical course, a long-lasting ICP elevation had not been present in any case. In the patients we investigated, the outcome was significantly correlated with the CO₂ reactivity values. These results show that the CO₂ reactivity measured initially already enables the prognosis to be appraised. The distinction between a CO₂ reactivity in excess of 2%ΔMFV/mm Hg PaCO₂ and a CO₂ reactivity of less than 2%ΔMFV/mm Hg PaCO₂ was crucial for the prognosis. Without exception, all patients with a CO₂ reactivity in excess of 2%ΔMFV/mm Hg PaCO₂ belonged to the group with GR or MD. In contrast, all patients with very unfavorable outcome (SD or PVS/DEAD) showed a CO₂ reactivity of less than 2%ΔMFV/mm Hg PaCO₂.

It might be argued that a decrease of ICP and a concomitant reactive rise of MFV occurs due to hyperventilation.\(^{21-23}\) In consequence of this rise in MFV, a false low CO₂ reactivity would be calculated, especially in patients with very high ICP values. However, in particular, these patients did not show a significant decrease of ICP in hyperventilation (Table 2). Thus, the greatly restricted CO₂ reactivity determined in these patients is to be regarded as real. Several studies have reported no appreciable effect of barbiturate administration on ICP in patients showing a reduction of CO₂ reactivity by more than 50% compared with a healthy control group.\(^{4,7}\) In our study, the average CO₂ reactivity of all patients was already reduced by 46% compared with the control group. Therefore, we consider that the general application of therapeutic hyperventilation and also barbiturate medication is problematic without prior determination of CO₂ reactivity. In our opinion, noninvasive TCD measurements of CO₂ reactivity in patients with severe cerebral disease and elevated ICP are easy to perform and provide useful information regarding the hemodynamic state, the cerebral vasoreactivity, and the prognosis. Knowledge of the CO₂ reactivity may enable a more exact determination of the possible beneficial effects of specific therapy and may therefore make a contribution to a better management of these critical patients.

References


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