Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: a transcranial Doppler study

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Object. Contemporary management of head-injured patients is based on assumptions about CO2 reactivity, pressure autoregulation (PA), and vascular reactivity to pharmacological metabolic suppression. In this study, serial assessments of vasoreactivity of the middle cerebral artery (MCA) were performed using bilateral transcranial Doppler (TCD) ultrasonography.

Methods. Twenty-eight patients (mean age 33 ± 13 years, median Glasgow Coma Scale score of 7) underwent a total of 61 testing sessions during postinjury Days 0 to 13. The CO2 reactivity (58 studies in 28 patients), PA (51 studies in 23 patients), and metabolic suppression reactivity (35 studies in 16 patients) were quantified for each cerebral hemisphere by measuring changes in MCA velocity in response to transient hyperventilation, arterial blood pressure elevation, or propofol-induced burst suppression, respectively. One or both hemispheres registered below normal vasoreactivity scores in 40%, 69%, and 97% of study sessions for CO2 reactivity, PA, and metabolic suppression reactivity (p < 0.0001), respectively. Intracranial hypertension, classified as intracranial pressure (ICP) greater than 20 mm Hg at the time of testing, was associated with global impairment of CO2 reactivity, PA, and metabolic suppression reactivity (p < 0.05). A low baseline cerebral perfusion pressure (CPP) was also predictive of impaired CO2 reactivity and PA (p < 0.01). Early postinjury hypotension or hypoxia was also associated with impaired CO2 reactivity (p < 0.05), and hemorrhagic brain lesions in or overlying the MCA territory were predictive of impaired metabolic suppression reactivity (p < 0.01). The 6-month Glasgow Outcome Scale score correlated with the overall degree of impaired vasoreactivity (p < 0.05).

Conclusions. During the first 2 weeks after moderate or severe head injury, CO2 reactivity remains relatively intact, PA is variably impaired, and metabolic suppression reactivity remains severely impaired. Elevated ICP appears to affect all three components of vasoreactivity that were tested, whereas other clinical factors such as CPP, hypotensive and hypoxic insults, and hemorrhagic brain lesions have distinctly different impacts on the state of vasoreactivity. Incorporation of TCD ultrasonography–derived vasoreactivity data may facilitate more injury- and time-specific therapies for head-injured patients.

Key Words • cerebral vasoreactivity • carbon dioxide reactivity • hyperventilation • intracranial hypertension • autoregulation • propofol • transcranial Doppler ultrasonography • traumatic brain injury
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and in whom and when to implement metabolic suppressive therapy. Although there have been numerous studies of posttraumatic vasoreactivity, in none have CO₂ reactivity, PA, and metabolic suppression reactivity been assessed in a combined and serial manner. In the present study we investigated these components of vasoreactivity by using TCD ultrasonography because it is a noninvasive method that allows simultaneous assessment of both cerebral hemispheres. Also, TCD has been shown to provide precise and reproducible assessments of CO₂ reactivity, PA, and metabolic suppression reactivity in healthy individuals and in patients with a variety of cerebral disorders. Specific objectives of this study included the following: 1) defining relative differences in the temporal pattern and degree of impairment for CO₂ reactivity, PA, and metabolic suppression reactivity; 2) determining whether known predictors of outcome after head injury are important determinants of impaired vasoreactivity; and 3) determining the impact of vasoreactive impairment on neurological outcome.

Clinical Material and Methods

Patient Population

This study included 28 patients receiving mechanical ventilation for moderate or severe head injury, who were admitted within 24 hours of injury to the UCLA Medical Center (26 patients) or Harbor–UCLA Medical Center (two patients) between August 1996 and March 2000. Patients were eligible if they were age 16 years or older; had sustained a closed or penetrating brain injury with abnormal findings on CT scans; had a postresuscitation GCS score of 3 to 12 (or deterioration to a GCS score ≤ 12), and required ICP monitoring.

General Management Protocol

Patients were admitted to the ICU after initial stabilization or surgical evacuation of an intracranial hematoma and were treated in accordance with a Level I Trauma Center protocol. Management goals included maintenance of ICP at less than 20 mm Hg and CPP greater than 70 mm Hg. Because of the occasional drift in ETCO₂ that occurred during PA testing, all flow velocities were corrected to an ETCO₂ of 34 mm Hg by using the patient’s own ventilatory breath.

Vasoreactivity Test Battery

Testing consisted of an assessment of right and left hemisphere CO₂ reactivity, PA, and metabolic suppression reactivity performed over a 2- to 3-hour period in the ICU. The first 10 patients studied underwent one or two clinical testing sessions, which consisted of a hyperventilation trial for CO₂ reactivity, followed by a transient phenylephrine-induced blood pressure elevation to assess PA. As described later, five of these initial patients also underwent a trial of metabolic suppression with propofol. The 18 subsequent patients were prospectively enrolled in the study, in which the goal was to perform a complete battery of vasoreactivity tests on postinjury Days 0, 1, 2, 4, 6, and 8. This protocol was approved by the institutional review boards of both the UCLA and Harbor–UCLA Medical Centers.

Physiological Parameters and TCD Ultrasonography

Recordings were made of the mean blood flow velocity of the right and left MCA and extracranial ICA by using a 2-MHz probe. These vessels were imaged using the temporal (MCA) and submandibular (extracranial ICA) windows according to the principles described by Auscell, et al. Continuous monitoring of bilateral MCA flow velocities for vasoreactivity testing was performed with a TCD unit similar to that used for conventional TCD studies (Neuroguard Cerebrovascular Diagnostic System; Nicolet Biomedical, Inc., Madison, WI) but equipped with an analog output device. Bilateral 2-MHz ultrasound transducers were fixed to an adjustable headband to prevent motion. The transducers were connected to a dedicated spectral analyzer that continuously calculated the mean V̇MCA. The V̇MCA represents the flow velocity of the MCA averaged over four cardiac cycles. The right and left V̇MCA, MAP, ICP, and ETCO₂ were continuously recorded. Data were sampled at a rate of 10 Hz but were averaged every 6 seconds to ensure independence of data points (that is, to account for the averaging of V̇MCA over four cardiac cycles and the calculation of ETCO₂ with each inspiratory breath).

Carbon Dioxide Reactivity

The mean V̇MCA was recorded during a 10-minute baseline monitoring period, followed by a 10-minute hyperventilation trial to lower ETCO₂ by 6 to 8 mm Hg. The change in arterial CO₂ was confirmed by arterial blood gas analysis. Studies were excluded from analysis if the ETCO₂ changed less than 3 mm Hg. In one case in which the patient’s baseline CBF was less than 30 ml/100 g/min, ETCO₂ was increased with hypoventilation to avoid inducing cerebral ischemia. Relative CO₂ reactivity was defined as the %Δ in mean V̇MCA per millimeter of mercury change in ETCO₂ (%ΔV̇MCA/mm Hg) as adapted from Klingelhofer and Sander. Based on their report, the normal range for CO₂ reactivity was defined as 3.7 %ΔV̇MCA/mm Hg.

Pressure Autoregulation

After completion of CO₂ reactivity testing and a 10-minute baseline monitoring period, PA was assessed by monitoring the response of V̇MCA to a phenylephrine-induced elevation in MAP of 10 to 15 mm Hg. Results were excluded from analysis if MAP changed less than 8 mm Hg. Because of the occasional drift in ETCO₂ that occurred during PA testing, all flow velocities were corrected to an ETCO₂ of 34 mm Hg by using the patient’s own hemispheric CO₂ reactivity values obtained during the
PA index was defined as a decrease in eCVR to blood pressure elevation (normal brovasculature. A negative PA index indicates a paradox-index of 0% indicates a completely pressure-passive cere-
complete compensatory change in eCVR, whereas a PA response to phenylephrine. A PA index of 100% indicates a burst suppression periods on electroencephalography,
10 minutes) and then titrated to achieve 6 to 10–second
started with a loading dose (1 mg/kg intravenously over
Metabolic Suppression Reactivity

After CO2 reactivity and PA testing were completed, re-
response to metabolic suppression was evaluated by mon-
tering the change in VMCA from baseline to electroencephalographically con-
defined burst suppression. Propofol (Diprivan, Astra Zéneca, Wilmington, DE) was chosen
rather than pentobarbital because the former has an ultra-
hort plasma halflife, it does not alter CO2 reactivity or PA,
and it is being increasingly used for sedation and ICP control in head-injured patients. Propofol was
started with a loading dose (1 mg/kg intravenously over
10 minutes) and then titrated to achieve 6 to 10–second
burst suppression periods on electroencephalography,
with a maximum infusion rate of 200 μg/kg/min. During
four study sessions in two patients, electroencephalography
was unavailable and propofol was increased to 160
to 200 μg/kg/min, which produces burst suppression in
the majority of individuals. Because infusions of metabol-
pressive agents such as propofol and pentobarbital often cause transient hypotension, a constant MAP was
maintained with phenylephrine delivered as needed dur-
ing propofol administration. Studies were excluded from
analysis if the MAP changed more than 10 mm Hg from
the baseline during induction of burst suppression. As
with PA testing, to account for changes in ETCO2 over the
course of propofol administration, all flow velocities were
corrected to an ETCO2 value of 34 mm Hg based on the pa-
tient’s own hemispheric CO2 reactivity values from the
same study session. A PA index was calculated as defined
by Tiecks, et al.59 The average MAP and VMCA before and
after the MAP change were used to calculate an eCVR1
and eCVR2 as follows: eCVR = MAP/VMCA. Autoregula-
tory capacity was defined as %ΔCVR%/ΔMAP from
MAP1 to MAP2, where %ΔCVR = (eCVR2 - eCVR1)/
eCVR1 and %ΔMAP = (MAP2 - MAP1)/MAP1.59 The
PA index was then calculated as the %ΔCVR%/ΔMAP in
response to phenylephrine. A PA index of 100% indicates a complete compensatory change in eCVR, whereas a PA
index of 0% indicates a completely pressure-passive cere-
brovasculature. A negative PA index indicates a paradoxical
decrease in eCVR to blood pressure elevation (normal
PA index was defined as ≳ 70%).59 During four study ses-
sions for two patients, MAP was decreased rather than in-
creased. These two patients had high baseline ICPs (mean
33 ± 8 mm Hg) during these study sessions and their ICPs
had been noted to increase with elevated MAP.

Metabolic Suppression Reactivity

After CO2 reactivity and PA testing were completed, re-
response to metabolic suppression was evaluated by mon-
tering the change in VMCA to propofol-induced electro-
cesencephalographically defined burst suppression. Propofol
(Diprivan, Astra Zéneca, Wilmington, DE) was chosen
rather than pentobarbital because the former has an ultra-
short plasma halflife, it does not alter CO2 reactivity or PA,
and it is being increasingly used for sedation and ICP control in head-injured patients. Propofol was
started with a loading dose (1 mg/kg intravenously over
10 minutes) and then titrated to achieve 6 to 10–second
burst suppression periods on electroencephalography,

TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Final</th>
<th>Probability</th>
<th>No. of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO2 reactivity: hyperventilation trial (58 studies in 28 patients)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETCO2</td>
<td>33.4 ± 4.6</td>
<td>25.7 ± 4.1</td>
<td>&lt;0.01</td>
<td>58</td>
</tr>
<tr>
<td>ICP</td>
<td>20 ± 11</td>
<td>13 ± 8</td>
<td>&lt;0.01</td>
<td>50</td>
</tr>
<tr>
<td>SjvO2</td>
<td>73 ± 8</td>
<td>67 ± 8</td>
<td>&lt;0.001</td>
<td>26</td>
</tr>
<tr>
<td>mean CO2 reactivity (normal ≳2.7% ΔVMCA/mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>104 ± 12</td>
<td>118 ± 13</td>
<td>&lt;0.001</td>
<td>51</td>
</tr>
<tr>
<td>CPP</td>
<td>88 ± 14</td>
<td>100 ± 16</td>
<td>&lt;0.001</td>
<td>47</td>
</tr>
<tr>
<td>ICP</td>
<td>17 ± 9</td>
<td>19 ± 9</td>
<td>&lt;0.01</td>
<td>47</td>
</tr>
<tr>
<td>mean metabolic reactivity (normal ≳70% ΔeCVR/%ΔMAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>107 ± 12</td>
<td>107 ± 11</td>
<td>NS</td>
<td>35</td>
</tr>
<tr>
<td>ICP</td>
<td>20 ± 11</td>
<td>17 ± 11</td>
<td>&lt;0.01</td>
<td>35</td>
</tr>
<tr>
<td>SjvO2</td>
<td>72 ± 9</td>
<td>75 ± 8</td>
<td>&lt;0.01</td>
<td>35</td>
</tr>
<tr>
<td>mean metabolic reactivity (normal ≳30% decrease in VMCA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>14 ± 13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The ETCO2, MAP, and ICP are all expressed in millimeters of mercury as the mean ± standard deviation. See Clinical Material and Methods for description of eCVR and VMCA.
† For CO2 reactivity, the mean MAP1 was 104 ± 14 and the MAP2 was 104 ± 13 (p = 0.76). In one CO2 reactivity study, in which the patient received hyperventilation (ETCO2 increased) because of low CBF, the initial and final ETCO2 values were switched for calculating the baseline and final ETCO2 values. The mean baseline and final ICP and SjvO2 values were based only on studies in which hyperventilation was used.
‡ In four PA studies in two patients, the MAP was lowered because of high ICP. In these four studies, the final and baseline values were switched for calculating the MAP1 and MAP2 values. The mean baseline and final CPP and ICP values were based solely on 47 studies in which MAP was elevated.

same study session. To assess the degree of interhemispheric differences for
CO2 reactivity, PA, and metabolic suppression reactivity in each individual, the hemisphere with the “better” and that
with the “worse” value was identified for each study. All

Hemispheric Asymmetry: Better Compared With Worse Hemispheres

To assess the degree of interhemispheric differences for
CO2 reactivity, PA, and metabolic suppression reactivity in each individual, the hemisphere with the “better” and that
with the “worse” value was identified for each study. All
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better and worse values were then normalized by dividing them by the lower limit of normal (2.7 for CO₂ reactivity, 70 for PA, and 30 for metabolic suppression) and multiplying by 100. These better and worse values were then compared. To assess interhemispheric differences in vasoreactivity studies further, interhemispheric (right compared with left) correlation analyses were performed for each type of vasoreactivity.

Predictors of Impaired Vasoreactivity: Global Factors

To determine the effects of patient age, GCS score, and hypotensive or hypoxic insults, the patients’ vasoreactivity scores for CO₂ reactivity, PA, and metabolic suppression reactivity were described in terms of global average (mean of right and left) of all studies performed, and worst global vasoreactivity score. For age, patients were categorized as being older or younger than 35 years of age, and for GCS score, patients were categorized as having an initial score of 3 to 5 compared with 6 or higher. Early hypotension or hypoxia was defined as a systolic blood pressure of less than 90 mm Hg, or a PaO₂ less than 60 mm Hg as well as intracerebral hematomas and contusions. The MCA territory was defined by conventional criteria as described by Osborn. Each hemisphere was categorized as with or without hemorrhagic lesions affecting the MCA territory. The mean hemispheric vasoreactivity scores over the postinjury period were then compared in affected and unaffected hemispheres.

The effect of MCA vasospasm was assessed by comparing hemispheres with and without vasospasm in terms of same-day ipsilateral CO₂ reactivity, PA, and metabolic suppression reactivity scores. Vasospasm in the MCA territory was defined by a mean VMCA of 120 cm/second or more, with a Lindgaard ratio of 3 or higher, where VMCA means flow velocity in the extracranial ICA.

Use of ICP and CPP as Predictors

Correlation analyses were performed comparing the global (mean of the right and left hemisphere) vasoreactivity scores for CO₂ reactivity, PA, and metabolic reactivity to baseline ICP and CPP immediately before beginning each respective component of the test battery. To assess the effect of intracranial hypertension in more depth, studies of CO₂ reactivity, PA, and metabolic reactivity were categorized as having a baseline ICP of less than or equal to 20 mm Hg or greater than 20 mm Hg and were then compared for mean global vasoreactivity scores.

Outcome and Vasoreactivity Scores

For all patients who had completed at least one vasoreactivity test battery and in whom a 6-month GOS score was available, a cumulative vasoreactivity score was derived. This score was based on whether global values for CO₂ reactivity, PA, or metabolic reactivity were in the normal range. Thus, on a given day a patient could have a cumulative vasoreactivity score of 0 (if all components were abnormal), up to a score of 3 (if all components were normal). The 6-month GOS score was then assessed as a function of this cumulative score. Both the first score (from the 1st day tested postinjury) and the average score (average of all study days) were analyzed as determinants of the GOS score.

Statistical Analysis

Most analyses involved multiple measurements over time for each individual. For these situations, continuous analyses were performed using mixed-effect linear regression models and categorical analyses were completed using mixed-effect logistic regression models. For the simpler situation of one observation per subject, continuous variables were compared using a t-test for independent or dependent variables, a Pearson correlation analysis for continuous variables, and a Spearman rank-order correlation analysis for noncontinuous variables. Multiple regression analysis was used to investigate the relation of age, GCS score, and hypotension/hypoxia to the global averages and worst global scores. Significance was defined at a probability of less than 0.05, but in some instances we call attention to results that are suggestive given the small sample sizes.

Results

The 28 patients had a mean age of 33 ± 13 years (range 17–63 years), a median postresuscitation GCS score of 7 (range 3–14), and 23 (82.1%) were men. Mechanisms of injury included motor vehicle accidents in 13 cases, falls in nine, gunshot wounds in two, automobiles striking pedestrians in two, a bicycle striking a pedestrian in one, and assault in one.

Number and Timing of Study Sessions

In total, 61 study sessions were performed in 28 patients. Study sessions occurred on postinjury Days 0 (eight sessions), 1 (11 sessions), 2 (13 sessions), 3 (five sessions), 4 (seven sessions), 5 (two sessions), 6 (seven sessions), 7 (one session), 8 (three sessions), 9 (three sessions), and 13 (one session). For temporal profile analysis, studies were combined within three time periods consisting of postinjury Days 0 to 1, postinjury Days 2 to 4, and postinjury Days 5 to 13, as was previously described by Martin et al. Sixteen patients underwent two to five study sessions and 12 patients were studied only once. Certain vasoreactivity studies were excluded from the final analysis for reasons outlined later. After accounting for excluded studies, a complete battery of vasoreactivity tests consisting of all three components (CO₂ reactivity, PA, and metabolic suppression testing) was performed in 32 of 61 study sessions in 14 patients.

Overall Status of Vasoreactivity

For each of the three components of the vasoreactivity battery, the baseline and final values for physiological parameters are shown in Table 1, and the numbers of stud-
ies and the numbers of patients with abnormal values are shown in Table 2 and Fig. 1.

**Carbon Dioxide Reactivity.** Sixty CO₂ reactivity tests were performed in 28 patients. Two studies from one patient were excluded from analysis because ETCO₂ changed less than 3 mm Hg. Calculated from the remaining 58 studies in 28 patients, the mean CO₂ reactivity was 3.3 ± 1.6 %ΔV̄/mm Hg. One or both hemispheres had below normal CO₂ reactivity in 40% of studies and the global average CO₂ reactivity was below normal in nine (32%) of 28 patients.

**Pressure Autoregulation.** Fifty-four PA trials were performed in 25 patients. Three studies in three patients were excluded because MAP changed less than 8 mm Hg; two patients were therefore excluded from this analysis, whereas the third, who had multiple studies, remained in the group. Calculated from the remaining 51 studies in 23 patients, the mean CO₂-corrected PA index was 67 ± 64%. One or both hemispheres had below normal PA in 69% of studies and the global average PA was below normal in 12 (52%) of 23 patients.

**Metabolic Suppression Reactivity.** Forty-four metabolic suppression studies were performed in 19 patients. Nine studies from six patients were excluded because the MAP changed more than 10 mm Hg from the baseline value during induction of burst suppression, leaving a total of 35 studies in 16 patients for our analysis. The mean metabolic suppression reactivity observed over all 35 studies was 14 ± 13%. One or both hemispheres had below normal reactivity in 97% of studies and the global average metabolic suppression reactivity was below normal in 15 (94%) of 16 patients.

**Temporal Changes in Vasoreactivity**

**Carbon Dioxide Reactivity.** Although considerable variability was seen in hemispheric CO₂ reactivity over time, the mean values were within the normal range for each of three time periods: 3.2 ± 1.9 %/mm Hg on postinjury Days 0 to 1 (38 hemispheres); 3.1 ± 1.3 %/mm Hg on postinjury Days 2 to 4 (48 hemispheres); and 3.8 ± 1.7 %/mm Hg on postinjury Days 5 to 13 (30 hemispheres). The mean hemispheric CO₂ reactivity tended to be higher on postinjury Days 5 to 13 compared with postinjury Days 2 to 4 (p = 0.3). There was also a trend for the percentage of studies with a normal global CO₂ reactivity to improve after postinjury Day 4: 57.9% on postinjury Days 0 to 1; 54.2% on postinjury Days 2 to 4; and 73.3% on postinjury Days 5 to 13 (p = 0.24; Fig. 2).

**TABLE 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Studies W/ 1 or Both Hemis &lt;Normal (%)§</th>
<th>Patients W/ GAR &lt;Normal (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ reactivity</td>
<td>23 of 58 (40)</td>
<td>9 of 28 (32)</td>
</tr>
<tr>
<td>PA</td>
<td>35 of 51 (69)</td>
<td>12 of 25 (52)</td>
</tr>
<tr>
<td>metabolic reactivity</td>
<td>34 of 35 (97)</td>
<td>15 of 16 (94)</td>
</tr>
</tbody>
</table>

* Significant at p < 0.0001 for studies and p = 0.002 for patients. Abbreviations: GAR = global average reactivity; hemis = hemisphere.
† Global average is the mean of the right and left hemispheres averaged over all study sessions for a given patient.
The correlation was poor between PA and CO2 reactivity (Pearson test: r = 0.013, p = 0.90; 96 hemispheres) and between PA and metabolic suppression reactivity (Pearson test: r = 0.018, p = 0.89; 66 hemispheres).

Hemispheric Asymmetry: Better Compared With Worse Hemispheres

As shown in Fig. 3, the mean normalized scores for better compared with worse hemispheres were 133% compared with 114% for CO2 reactivity, 120% compared with 71% for PA, and 62% compared with 31% for metabolic suppression reactivity. On average there was minimal asymmetry for CO2 reactivity, with both hemispheres above the lower threshold of normal. For PA, the better hemisphere, on average, was normal and the worse hemisphere was impaired. For metabolic suppression reactivity, both better and worse hemispheres were severely impaired. The relative degree of asymmetry is further demonstrated by analysis of the interhemisphere correlations. These were 0.90 (SE 0.05) for CO2 reactivity, 0.72 (SE 0.10) for PA, and 0.62 (SE 0.14) for metabolic suppression reactivity. The interhemisphere correlation for CO2 reactivity (0.90) was significantly stronger than for PA (0.72) and metabolic suppression reactivity (0.62) (p = 0.03).

Table 3: Summary of predictors of impaired vasoreactivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age</th>
<th>GCS Score</th>
<th>H/H</th>
<th>ICP</th>
<th>CPP</th>
<th>MCA Lesions</th>
<th>Vaso- spasms</th>
</tr>
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<tbody>
<tr>
<td>CO2 reactivity</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>PA</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>metabolic reactivity</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

* See Predictors of Impaired Vasoreactivity in the Methods section for how each parameter was assessed in relation to status of vasoreactivity. Abbreviations: H/H = hypotension/hypoxia; hem = hemorrhagic.
In this study of moderately and severely head injured patients, serial TCD assessments of vasoreactivity within the first 2 weeks after injury revealed significant differences in the degree of impaired CO$_2$ reactivity, PA, and metabolic suppression reactivity. On average, CO$_2$ reactivity remained relatively intact and tended to improve further over time, and PA was variably impaired over time, whereas metabolic suppression reactivity remained severely depressed. Regarding the interrelationships between these vasoreactive components, there was only a weak correlation between same-day, same-side CO$_2$ reactivity and metabolic suppression reactivity, and poor correlations between PA and CO$_2$ reactivity and between PA and metabolic reactivity. There were also often large hemispheric differences in vasoreactivity studies for metabolic suppression reactivity and PA, but such differences were typically minor for CO$_2$ reactivity. Intracranial hypertension was the only factor associated with impairment of all three vasoreactivity components, whereas a lower baseline CPP correlated with impaired CO$_2$ reactivity and PA. Selective impairment of CO$_2$ reactivity was seen in individuals with early hypotensive or hypoxic insults. Similarly, hemorrhagic lesions in or overlying the MCA territory were associated with selective impairment of ipsilateral metabolic suppression reactivity. Finally, the overall degree of vasoreactive impairment as defined by a cumulative vasoreactivity score correlated with the 6-month GOS score. These findings are discussed later in relation to previous studies of postraumatic vasoreactivity and their potential clinical significance.

**Methodological Issues**

Transcranial Doppler ultrasonography is an established method of estimating moment-to-moment changes in CBF and, although indirect, it is based on substantial evidence that the cross-sectional area of the large-caliber vessels of the circle of Willis from which the TCD signal is derived does not change significantly during fluctuations in blood pressure and PaCO$_2$. Blood flow velocity changes in the insonated vessels are therefore proportional to changes in CBF. The strong correlation between the calculated CO$_2$ reactivity and the decrease in SjvO$_2$ during hyperventilation in our study further supports the concept that the change in TCD velocity is a true surrogate of the relative change in CBF. Given that this study involved the repeated performance of a lengthy three-part battery of tests for

**Illustrative Case**

This 20-year-old man suffered a self-inflicted gunshot wound. His initial GCS score was 5 and a CT scan revealed a bullet track coursing through the right temporal lobe with bilateral SAH and a right temporal hematoma requiring evacuation (Fig. 4 upper left). Vasoreactivity testing was performed on postinjury Days 0, 1, 2, and 6. As seen in Fig. 4 upper right, CO$_2$ reactivity was abnormal on postinjury Days 0 and 1, but normalized by postinjury Day 2. His PA and metabolic reactivity remained abnormal throughout the first 6 days (Fig. 4 lower). For all three vasoreactivity parameters, the greatest degree of right/left asymmetry was seen on postinjury Day 0, particularly for metabolic reactivity. Although the left hemisphere demonstrated an appropriate decrease in MCA flow velocity in response to propofol-induced burst suppression, the more severely injured right hemisphere displayed a paradoxical increase in flow velocity (Fig. 5).
vasoreactivity, TCD ultrasonography was considered the ideal modality. In contrast, traditional methods of quantitating vasoreactivity with serial CBF measurements, such as the $^{133}$Xe bedside technique or Xe-CT, were deemed clinically unsuitable. Another advantage of TCD ultrasonography for this study was that discrete data were provided for each hemisphere that could then be related to focal abnormalities within the MCA territory.

Because multiple factors affect CBF in intubated patients, considerable effort was made to control these factors during vasoreactivity testing. Given that CO$_2$ reactivity was typically preserved in these patients, even relatively minor fluctuations in ETCO$_2$ could result in significant changes in MCA velocity that in turn would affect the final calculated PA index or metabolic suppression reactivity. This potential problem was minimized by correcting all flow velocities to an ETCO$_2$ of 34 mm Hg by using the patient’s own hemispheric CO$_2$ reactivity values obtained during the same study session.

Similarly, because PA was often impaired, nine metabolic suppression studies were excluded when MAP changed by more than 10 mm Hg from the baseline value. With few exceptions, previous vasoreactivity studies and reports on pharmacological metabolic suppression have not corrected for changes in CO$_2$ or blood pressure or excluded studies in which significant fluctuations in PaCO$_2$ or blood pressure occurred. For example, in the study by Cormio, et al., of 67 severely head injured patients, induction of pentobarbital coma resulted in a mean decrease in ICP and MAP of 12 and 9 mm Hg, respectively. In our study, in which a relatively constant blood pressure was maintained with a phenylephrine infusion, induction of a propofol coma resulted in a mean decrease in ICP of 3 mm Hg.

The use of phenylephrine to prevent propofol-induced systemic hypotension and the resultant cerebral hypoperfusion that is independent of propofol’s metabolic effects was thought to be justified and necessary. Adrenergic agents appear to blunt the hypotensive effect of agents like propofol by causing peripheral vasoconstriction without significant direct cerebrovascular effects, even after head injury. In a TCD ultrasonography study by Strebel, et al., conducted in healthy individuals who were anesthetized with propofol, phenylephrine and norepinephrine had no effect on MCA flow velocity despite a 20% increase in MAP. In a cortical contusion injury study by Cherian, et al., early postinjury infusion of phenylephrine increased CBF in the pericontusional area and contralateral hemisphere but only in proportion to the increase in MAP and CPP.

For several clinical reasons, including high ICP, low CBF, hemodynamic instability, and neurological improvement, complete batteries of tests for vasoreactivity could not be obtained over multiple days in all patients; however, the statistical analyses used accounted for variable numbers of studies nested within subjects. As more patients are evaluated with this TCD-based battery of tests, a clearer picture of the time course and predictors of vasoreactive impairment should be delineated.

Reactivity of CO$_2$

In previous studies it has been demonstrated that CO$_2$
reactivity is often impaired in the early stages after head injury and then generally recovers after 4 to 7 days. In two reports of severely head injured patients studied within 4 days of injury, globally impaired CO₂ reactivity was documented in 44% of subjects by using the ¹³³Xe method to measure CBF, and regionally impaired CO₂ reactivity was seen in more than 90% of patients tested with Xe-CT. In our study, global CO₂ reactivity was below normal in 55% of studies performed on postinjury Days 0 to 4; however, after Day 4, CO₂ reactivity was below normal in only 25% of patients. The most important clinical determinants of the state of CO₂ reactivity appear to be the baseline ICP and CPP, as well as early postinjury hypertension or hypotension. A similar relationship between ICP and CO₂ reactivity was shown in the TCD study by Klingelhöfer and Sander.27 Despite the association of high ICP with impaired CO₂ reactivity in the present study, hyperventilation resulted, on average, in a highly significant decrease in ICP.

Pressure Autoregulation

Using the ¹³³Xe method, disturbed PA has been seen in 31 to 50% of severely head injured patients during the first 10 days after trauma. Impaired regional PA, either transient or persistent, was detected in 81% of 26 patients studied within 2 weeks of injury by Lam et al., who used laser Doppler flowmetry for their investigation. Our study also indicates that the temporal pattern of PA over the first 2 weeks postinjury varies across patients and does not consistently improve over time. As with CO₂ reactivity, the baseline ICP and CPP appear to be important determinants of altered autoregulation.

Interestingly, impaired PA was observed in almost two thirds of studies in patients with a baseline CPP of over 70 mm Hg. Additionally, on average, blood pressure elevation resulted in a significant albeit relatively small increase in ICP. These findings indicate that even though a higher CPP may favorably influence the state of PA, in the majority of instances, maintaining CPP above 70 mm Hg does not ensure normal PA. In patients with impaired PA, induced blood pressure elevation may result in hyperemia and worsening of intracranial hypertension.

Metabolic Suppression Reactivity

In previous studies it has been shown that CO₂ reactivity correlated strongly with the ICP response to barbiturates. In the present study, however, we found only a weak correlation between same-day, same-hemisphere CO₂ reactivity and metabolic responsiveness to propofol. On average, propofol-induced electroencephalographically confirmed burst suppression resulted in only a 14% decrease in mean flow velocity, a value less than half the blood flow velocity decrease normally seen in healthy individuals and animals. This blunted response to high-dose propofol is likely in part related to the fact that global cerebral oxidative and glucose metabolism are already markedly depressed during the first 2 weeks after moderate or severe head injury. Our study, however, also shows that other factors, including high ICP, ICH, and possibly vasospasm, may contribute to the degree of impaired metabolic responsiveness. This association of impaired metabolic suppression reactivity to ipsilateral ICH may be related to injury-induced release of vasoactive factors such as adenosine.

Outcome and Vasoreactivity

Previous studies have linked poor neurological outcome after head injury with impairment of CO₂ reactivity, PA, and responsiveness to metabolic suppression therapy. Our investigation is unique in combining all three vasoreactive components to derive a cumulative vasoreactivity score. By so doing, a relatively strong correlation in 13 patients was found between this score and the 6-month GOS score. Admittedly, these findings are preliminary and warrant validation with a larger patient population that incorporates other known prognostic indicators in a multivariate statistical model.

Clinical Use of Vasoreactivity Data

This TCD-based battery of tests is being increasingly used to optimize and individualize ICP and CPP therapy in our daily management of head-injured patients. For example, individuals with poorly controlled intracranial hypertension, high SjvO₂, and impaired PA are often effectively managed with judicious blood pressure reduction resulting in CPPs of 50 to 60 mm Hg and SjvO₂ values in the 60 to 70% range. Similarly, in patients with impaired metabolic suppression reactivity but relative preservation of CO₂ reactivity, high-dose propofol or pentobarbital can be used to minimize metabolic demands while aggressive hyperventilation is used to lower ICP. In such instances, PaCO₂ is often reduced to 25 mm Hg, provided that SjvO₂ remains above 60%. The overall effectiveness of more targeted treatments such as these in improving outcome after head injury remains to be proven.

Conclusions

This TCD-based study demonstrates markedly different degrees of impairment of CO₂ reactivity, PA, and meta-
Vasoreactivity changes after head injury

Reactive suppression activity during the first 2 weeks after moderate or severe head injury. The relative degree of normalcy and the trend toward further improvement in CO₂ reactivity contrasts with the more variable pattern of PA and the persistent depression of metabolic suppression reactivity. Incorporating vasoreactivity data into the ICU management of head-injured patients will hopefully facilitate more targeted use of current and future ICP and CPP therapies.

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References

38. Martin NA, Patwardhan RV, Alexander MJ, et al: Charac-
terization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia and vasospasm. J Neurosurg 87:9–19, 1997


