Cerebrovascular Carbon Dioxide Reactivity and Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

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Objective: To determine the predictors of impaired cerebrovascular reactivity (CVR) and the value of CVR in predicting delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH).

Design: Prospective observational study. We evaluated CVR during the following intervals: period 1, SAH days 0 to 3; period 2, SAH days 4 to 7; and period 3, SAH days 8 to 10. Normal CVR was defined as an increase in mean blood flow velocity of at least 2% per 1–mm Hg increase in PCO2.

Setting: Neurointensive care unit of the Columbia Presbyterian Medical Center.

Patients: Thirty-four consecutive patients with acute SAH who underwent measurement of changes in the middle cerebral artery mean blood flow velocity after carbon dioxide challenge.

Main Outcome Measure: Occurrence of DCI.

Results: Delayed cerebral ischemia occurred in 10 patients (29%). Impaired CVR was more frequent in patients with a poor clinical grade on admission and at the time of examination. During period 1, there was only a trend toward lower CVR in patients who later developed DCI (1.1% vs 1.9% per 1–mm Hg increase in PCO2; P = .07). However, those who developed DCI had progressively lower CVR during periods 2 (0.7%/mm Hg vs 2.1%/mm Hg; P < .001) and 3 (0.6%/mm Hg vs 2.4%/mm Hg; P < .001). Independent predictors of DCI included a decrease in CVR between periods 1 and 2 (P = .03) and a poor Hunt-Hess score (P = .04). Impaired CVR at any point had a sensitivity for subsequent DCI of 91% and a specificity of 49%.

Conclusions: Impaired CVR in response to carbon dioxide challenge is frequent after SAH, particularly in patients with a poor clinical grade. Progressive loss of normal CVR identifies patients at high risk for DCI, and persistently normal reactivity implies a low risk.

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SYMPTOMATIC VASOSPASM IS A serious complication of aneurysmal subarachnoid hemorrhage (SAH). From 20% to 40% of patients will develop neurological deficits or infarction due to delayed cerebral ischemia (DCI). Transcranial Doppler ultrasonography (TCD) is widely used to monitor the course of vasospasm after SAH, but its ability to predict DCI based on the presence of elevated mean blood flow velocities (mBFV) or Lindegaard ratios alone remains limited.

Cerebrovascular reactivity (CVR) reflects the normal compensatory dilatatory capacity of cerebral arterioles in response to a stimulus such as carbon dioxide (CO2) or acetazolamide sodium. By evaluating this functional property of the cerebral vasculature using changes in cerebral blood flow or cerebral blood flow velocities, previous studies have tried to demonstrate an association between a progressive impairment of CVR and the subsequent development of DCI. These studies have showed conflicting results, however. Specifically, CVR testing by means of TCD and CO2 challenge during the acute and chronic phases of SAH has been found to have an inconsistent relationship with DCI. Accordingly, recent guidelines have stated that no recommendations can be made about the use of CVR to predict DCI after aneurysmal SAH.

In this study, we performed sequential measurements of CO2 CVR assessed by TCD to determine the predictor of impaired CVR after acute SAH and whether change in CVR in the first days after SAH can predict DCI.

METHODS

STUDY POPULATION

We prospectively studied 34 consecutive patients with aneurysmal SAH who were admitted to the neurointensive care unit of...
the Columbia Presbyterian Medical Center from April 1, 2007, through May 30, 2008. Transcranial Doppler ultrasonography was performed once during each of the following 3 intervals: period 1, SAH days 0 to 3; period 2, SAH days 4 to 7; and period 3, SAH days 8 to 10. No CVR testing was performed after the diagnosis of DCI. Written informed consent for participation in a prospective observational cohort study was obtained from the patient or a surrogate, and the study was approved by the local institutional review board. The diagnosis of SAH was established by the admission computed tomography (CT) or by the presence of blood and xanthochromia in the cerebrospinal fluid. Criteria for inclusion in the present analysis consisted of the successful performance of at least 1 TCD CO2 CVR test during the postoperative period. Patients with SAH due to trauma, arteriovenous malformation, mycotic aneurysm rupture, sympathomimetic drug exposure, vasculitis, or other causes were excluded. Cerebrovascular reactivity testing was not performed in patients who lacked adequate TCD windows or had recurrent intracranial pressure (ICP) elevations of more than 20 mm Hg or after the onset of DCI. Patients with high-grade (>70%) carotid stenosis were also excluded because of the possibility that impairment in CVR would be due to proximal carotid disease rather than hemorrhage.

CLINICAL AND RADIOLOGICAL VARIABLES

We prospectively recorded baseline demographic information and clinical and radiological findings. Neurological status on admission and at the time of examination was assessed with the Hunt-Hess and Glasgow Coma Scale scores. Admission head CT was evaluated to determine the modified Fisher score22 and the Hijdra SAH score.23 Follow-up brain imaging was performed as clinically indicated. Angiography was performed on admission to locate the aneurysm and when symptomatic vasospasm was suspected. The calendar day of SAH onset was referred to as SAH day 0.

CLINICAL MANAGEMENT

All patients received 0.9% normal saline at a rate of 1 mL/kg per hour and supplemental 5% albumin solution to maintain central venous pressure of more than 5 mm Hg. Intracranial hypertension and acute symptomatic intracranial mass effect were treated with repeated boluses of 20% mannitol (0.25–1.50 g/kg) or 23.4% hypertonic saline solution (0.5–2.0 mL/kg). In patients with persistent mass effect related to cerebral edema, 3% sodium acetate solution was given to maintain serum osmolality at 320 mOsm/L. Persistent fever (temperature exceeding 38.3°C) was treated with acetaminophen and cool-mist nebulization. Blood transfusions were given to maintain hemoglobin levels at more than 7.0 mg/dL (to convert to grams per liter, multiply by 0.01), except in the presence of ongoing cerebral or cardiac ischemia, in which case a target hemoglobin level of more than 10.0 mg/dL was maintained. Hypertensive hypervolemic therapy was initiated only after the diagnosis of DCI. Therefore, none of the CVR testing was influenced by this treatment.

TCD AND CVR TESTING

All patients first underwent a complete TCD study with the use of a handheld 2-MHz pulse-wave probe (Pioneer 8080; Nicolet Biomedical, Madison, Wisconsin) by 1 of 2 examiners (E.C. and P.K.). Two probes were then fixed bilaterally using a head frame (Nicolet Biomedical) to perform bilateral continuous monitoring of middle cerebral artery mBFV. End-tidal CO2 level was continuously measured by means of an infrared capnometer (9004-Capnocheck; BCI, Waukesha, Wisconsin) connected to a 2-way valve face mask or the ventilator circuit in intubated patients. After 2 minutes of stable baseline mBFV values, 5% CO2-enriched air was administered. Cerebrovascular reactivity was calculated as the percentage of increase in mBFV per 1–mm Hg increase in end-tidal CO2 level. Overall, the average length of the CVR examination, including setup, was about 15 minutes. A 6–mm Hg absolute increase in end-tidal CO2 level was required for a valid CVR calculation. Normal CVR was predefined as an increase in middle cerebral artery mBFV of at least 2% per 1–mm Hg increase in end-tidal CO2, based on normative data performed at our institution.24 Arterial blood pressure, heart rate, and ICP were recorded at baseline and during CO2 testing. The following adverse effects were recorded: headaches, palpitations, and increased ICP.

OUTCOME

The primary outcome measure was DCI, defined as (1) clinical deterioration (ie, a new focal deficit, a decrease in level of consciousness, or both), or (2) a new infarct on CT that was not visible on the admission or immediate postoperative CT because of vasospasm. Other potential causes of clinical deterioration or CT lucencies, such as hydrocephalus, rebleeding, cerebral edema, retraction injury, ventriculitis, metabolic derangements, and seizures, were rigorously excluded. Evidence of arterial spasm by angiography was confirmed in all cases. We used this definition of DCI (combining radiological and clinical pattern) because it was shown in a recent publication25 to have a better predictive value than (1) clinical deterioration only due to vasospasm, (2) angiographic vasospasm irrespective of clinical status, or (3) TCD mBFV of more than 120 cm/s.

STATISTICAL ANALYSIS

Cerebrovascular reactivity and mBFV for the right and left sides were averaged, resulting in a single CVR and mBFV value for each test. We first determined the impact of CO2 inhalation on blood pressure, heart rate, ICP, and cerebral perfusion pressure. We then determined the clinical, radiological, and physiological predictors of impairment of CVR dichotomized into normal or abnormal using the threshold of normal CVR predefined as an increase in middle cerebral artery mBFV of at least 2%/mm Hg, based on normative data performed at our institution.24 In addition to the evolution of CVR between periods 1 and 2, we then identified clinical, radiological, and physiological predictors of DCI. Those with significant univariate associations (P < .05) were evaluated in a forward stepwise multivariate logistic regression model to identify independent associations. We used the χ2 or Fisher exact test for dichotomized variables. Continuous variables were tested using a 2-tailed t test or a Mann-Whitney test. All probability values were 2-tailed and considered significant if less than .05. Finally, the sensitivity, specificity, and positive and negative predictive values to predict DCI of an abnormal CVR during any of the period values were then determined.

RESULTS

STUDY POPULATION

Baseline characteristics of the 34 patients are listed in Table 1. Eighty-three CVR tests were performed
During CO2 inhalation, mean (SD) ICP significantly increased (102 [19] to 101 [21] mm Hg; no significant changes in mean (SD) arterial blood pressure (11 [4] to 19 [10] mm Hg; P=.09). There was a nonsignificant trend toward a higher mBFV during period 2 in patients who later developed DCI compared with those who did not (1.1%/mm Hg vs 0.6%/mm Hg; P=.01). Those who developed DCI had progressively lower CVR during periods 2 (0.7%/mm Hg vs 2.1%/mm Hg; P=.01) and 3 (0.6%/mm Hg vs 2.4%/mm Hg; P<.001). Baseline mBFV during period 1 was similar. There was a trend toward a higher mBFV during period 2 in patients who subsequently developed DCI (95 vs 65 cm/s; P=.09; Figure 1). This difference was less apparent during period 3.

TABLE 1. Baseline Characteristics of the 34 Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54 (16)</td>
</tr>
<tr>
<td>Women</td>
<td>26 (76)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Hunt-Hess score</td>
<td></td>
</tr>
<tr>
<td>1 (Mild headache)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>2 (Severe headache)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>3 (Lethargic or confused)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>4 (Stupor)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>5 (Coma)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Aneurysm size, mean (SD), mm</td>
<td>6.8 (4.6)</td>
</tr>
<tr>
<td>Modified Fisher CT score</td>
<td></td>
</tr>
<tr>
<td>0 (No blood)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>1 (Thin SAH, no IVH)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>2 (Thin SAH, bilateral IVH)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>3 (Thick SAH, no IVH)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>4 (Thick SAH, bilateral IVH)</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

Overall: 30 during period 1, 29 during period 2, and 24 during period 3. Nineteen studies (23%) were performed during mechanical ventilation and 64 (77%) with a face mask. Delayed cerebral ischemia occurred in 10 patients (29%): 9 experienced clinical deterioration and 2 developed infarction (1 patient had both). Onset of DCI symptoms occurred a median of 7 (range, 4-10) days after SAH onset. The median latency between CVR deterioration and DCI was 1.5 (range, 4-10) days after SAH onset. The median duration of patients.

EFFECTS OF CO2 CVR ON PHYSIOLOGICAL VARIABLES

During CO2 inhalation, mean (SD) ICP significantly increased (11 [4] to 19 [10] mm Hg; P=.002). There were no significant changes in mean (SD) arterial blood pressure (102 [19] to 101 [21] mm Hg; P=.40) or heart rate (82 [15] to 85 [15] bpm; P=.10).

PREDICTORS OF IMPAIRED CVR

Fifty-one of the 83 middle cerebral artery CVR examinations (61%) showed impaired CVR (<2% increase of middle cerebral artery mBFV per 1–mm Hg increase in end-tidal CO2 level). The only predictors of impaired reactivity were poor Hunt-Hess score on admission and coma (Glasgow Coma Scale score, ≤8) on the day of examination (Table 3). There was a nonsignificant trend toward higher age and heart rate in patients impaired CVR. No associations between impaired CVR and the extent of subarachnoid or intraventricular blood on the admission CT were observed.

TIME COURSE OF CVR IN RELATION TO DCI

During period 1 (SAH days 0-3), there was a trend toward a lower CVR in patients who subsequently developed DCI compared with those who did not (1.1%/mm Hg vs 1.9%/mm Hg CO2; P=.07). Those who developed DCI had progressively lower CVR during periods 2 (SAH days 4-7) and 3 (SAH days 8-10), whereas those who did not develop DCI normalized their CVR during periods 2 (0.7%/mm Hg vs 2.1%/mm Hg; P<.001) and 3 (0.6%/mm Hg vs 2.4%/mm Hg; P<.001). Baseline mBFV during period 1 was similar. There was a trend toward a higher mBFV during period 2 in patients who developed DCI (95 vs 65 cm/s; P=.09; Figure 1). This difference was less apparent during period 3.

PREDICTORS OF DCI

Predictors of DCI in the univariate analysis are presented in Table 3. In the multivariate analysis (including abnormal CVR and Hunt-Hess score [3-5]), a decrease in CVR between periods 1 and 2 was independently associated with DCI (odds ratio, 0.149; 95% confidence
interval, 0.03-0.86 [P = .03]), as well as a Hunt-Hess score ranging from 3 to 5 (odds ratio, 24.9; 95% confidence interval, 1.3-496.7; P = .04).

**PROGNOSTIC VALUE OF IMPAIRED CVR**

When all presymptomatic TCD reactivity examination findings were evaluated, the presence of impaired CVR (<2%/mm Hg) at any point had a sensitivity for subsequent DCI of 91%, a specificity of 49%, a positive predictive value of 39%, and a negative predictive value of 92%. The area under the receiver operating characteristic curve (Figure 2) predicting DCI across the range of possible CVR thresholds was 0.85, suggesting a good accuracy of this diagnostic test.

**COMMENT**

In this study, we found that CO₂ CVR progressively fell in patients with SAH who developed DCI and that an abnormal CO₂ CVR was more frequent in patients with clinically severe SAH.

Cerebrovascular reactivity was impaired during period 1 in most of the patients we studied. In those who did not develop DCI, CVR progressively normalized, whereas CVR declined even further among patients who developed DCI. Our results showed that successive measurements of CVR can help to determine the course of arterial vasospasm and subsequent risk of DCI because a decrease in CVR was independently associated with the occurrence of DCI. These findings, based on a noninvasive method performed at the bedside, are consistent with previous studies using invasive brain monitoring that showed that progressive impairment of cerebral autoregulation and brain tissue oxygen reactivity occur before the onset of DCI in patients with SAH.

An abnormal CVR at any time during the study was independently associated with the development of subsequent DCI. The sensitivity of impaired CVR to...
predict DCI was 91%, with a negative predictive value of 92%, suggesting that most patients with DCI will have an impaired CVR and that a normal test result is useful to exclude the disease. The area under the receiver operating characteristic curve of CVR for the occurrence of DCI was 0.85, suggesting a good accuracy of this test.

The pathophysiological mechanisms underlying impairment of CVR and autoregulation in patients with DCI remain uncertain. Previous experiments suggest a deleterious role of hemoglobin and other blood-derived metabolites, with trapping of nitrous oxide, endothelium-mediated vasoconstriction, and impaired endothelium-dependent vasodilatory responses.22-25 Our results suggest that the pathophysiological mechanisms related to microcirculatory dysfunction begin very early in the course of the disease. On the contrary, mBFV elevations indicative of large vessel spasm were most prominent during period 2. Although our study was not designed to determine the predictive value of mBFV, the relatively weak relationship between elevated mBFV and DCI that we observed is consistent with previous studies showing the limited predictive value of TCD velocity elevations in the acute phase of SAH.25

A decrease of CVR below the normal range, defined as an increase of middle cerebral artery mBFV of less than 2%/mm Hg CO₂, was found in nearly two-thirds of the recordings. Cerebrovascular reactivity dysfunction was particularly frequent within 3 days after SAH, especially among patients with a poor clinical grade. This suggests that vasomotor dysfunction is a frequent and early consequence of acute SAH and is not exclusively a delayed downstream consequence of large artery vasospasm. In contrast to a previous study of CVR in acute SAH,37 elevation of mBFV was not associated with reduced CVR, possibly because we did not restrict our study to the patients with good Hunt-Hess scores. In contrast to the findings of others,22,23 the amount and location of subarachnoid and intraventricular hemorrhage were not associated with impaired CVR.

In our patients, CVR testing induced a transient but significant increase in ICP, reflecting an increase of cerebral blood volume secondary to vasodilation of cerebral arteries.32,33 But the cerebral perfusion pressure did not decrease significantly. The effect of CO₂ was limited to the cerebral circulation because no changes were found in the arterial blood pressure or heart rate, contrary to what has been previously described.34

Clinically, our study suggests that CVR testing may be a useful monitoring tool in the routine management of the acute phase of SAH, when the patients are most likely to develop angiographic vasospasm and DCI. Overall, the sensitivity of CVR was high, suggesting that, despite lower specificity and positive predictive values, this technique is mainly useful to exclude the diagnosis of DCI in patients presenting with normal CVR. Compared with previous reports, our results, which are based on a larger population and more data measurement points, emphasize the potential value of sequential assessment of CVR. Indeed, the sequential measurement of CVR demonstrated that a decrease in CVR between days 0 to 3 and 4 to 7 is an independent predictor of DCI. Although we did not perform CVR testing on a daily basis, the lag between the diagnosis of CVR deterioration and the diagnosis of DCI was 1.5 days, enough time to institute preventive measures to avoid DCI.

Several limitations of this study deserve attention. First, the study sample was small. Second, a significant increase of ICP during CVR testing was found but without a significant drop in cerebral perfusion pressure. To avoid potential complications of CVR testing, continuous monitoring and attention to ICP are required in patients at risk for intracranial hypertension. Cerebrovascular reactivity testing with use of a face mask requires a certain level of cooperation in nonintubated patients. Third, we did not correct for the effects of sedatives or vasoactive agents that could affect CVR. However, the impact of vasoactive agents may be considered limited because hypervolemic hypertensive treatment was initiated only after the diagnosis of DCI in our population and because all our CVR testing was performed before DCI. Fourth, we averaged CVR from both sides to give a global measure of the vasospastic condition because vasospasm may be multifocal or may affect a vessel other than middle cerebral arteries, the only vessels investigated. In addition, we compared CVR with mBFV but not with other established TCD criteria such as the Lindegaard ratio or elevation of mBFV of more than 50 cm/s daily. Finally, it is true that the study team was aware of the TCD-CVR data when adjudicating the diagnosis of DCI. However, TCD values were only 1 consideration in diagnosing DCI; we also evaluated CT, CT angiography, magnetic resonance images, and angiography, as well as the clinical features of the syndrome, response to treatment, and laboratory test results. Furthermore, in our study, a single abnormal CVR reading had a low specificity, suggesting that the diagnosis of DCI cannot be established on the basis of a single CVR value. Before the study was completed, we did not know that the progressive decrease in CVR would be an independent predictor of DCI.

In summary, our data indicate that successive CO₂ CVR testing is a potentially useful adjunct to routine TCD monitoring after SAH. In this study, the presence of abnormal CVR (<2%/mm Hg) at any point was associated with DCI, with 91% sensitivity and a 39% positive predictive value. Even more notable, the decline in CVR in the acute phase is an independent predictor of subsequent DCI. Our results suggest that successive CO₂ CVR may be useful as a routine component of cerebrovascular monitoring in patients with SAH.

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Author Contributions: Dr Carrera had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design. Carrera, Kurtz, Badjatia, Claassen, Lee, Marshall, and Mayer. Acquisition of data: Carrera, Kurtz, Fernandez, Lee, and Schmidt. Analysis and interpretation of data: Carrera, Kurtz, Badjatia, Claassen,

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