The Prognostic Value of Noninvasive CBF Measurement in Subarachnoid Hemorrhage

Gilles Géraud, M.D., Michel Tremoulet, M.D., Antonio Guell, M.D., and André Bes, M.D.

SUMMARY Seventy-four measurements of cerebral blood flow (CBF) were performed using the Xenon 133 inhalation method in 50 cases of spontaneous subarachnoid hemorrhage. This method is non-traumatic, reproducible and dependable. A correlation was found between clinical condition and CBF values, but in a number of cases which cannot be dismissed, very low mean CBF values or ischemic foci were revealed when clinical state gave no indication of same. A poor correlation appeared between vasospasm seen by angiography and ischemic foci detected by isotopic technique. Patients' age influenced CBF values but not clinical evolution.

CBF values, measured in the first two weeks of illness, were significantly higher in those patients having favorable outcome, whatever their clinical state at the time of CBF measurement (comas excluded). The figure of 60 ml/100g/min. for mean cortical flow seemed to be a critical level below which risk of complications was greater. Conversely, in every case where mean cortical flow measured above 70 ml/min. outcome was favorable. Thus, CBF measurement promises to be a valuable prognostic tool, playing an important role in the therapeutic strategy for this type of patient.

Materials and Methods

Fifty patients (20 men, 30 women) with subarachnoid hemorrhage were studied. Mean age of the subjects was 48 ± 12 years (ranging from 21 to 68 years of age). The neurological condition of the patients was graded according to the Hunt and Hess criteria: Grade I and II, asymptomatic headache without alteration of consciousness or neurological deficit (29 cases); Grade III, drowsiness or confusion (14 cases); Grade IV stupor with moderate-to severe hemiparesis. Grade IV comatose patients were excluded from this study. The grading of patients occurred at the time of CBF measurement.

An angiogram was performed on each patient: in 39 cases out of 50 it revealed 1 or more aneurysms. In 11 cases, the aneurysm was situated on the intracranial carotid; in 11 others, on the anterior communicating artery; in 5 cases, on the middle cerebral artery bifurcation; in 7 cases on another artery; and in 5 cases several aneurysms were found. Vasospasm was discovered in 19 patients (38%); 9 localized and moderate cases, 7 multifocal cases, 3 diffuse cases. CT scan was performed on 35 patients and showed blood present in the basal cisterns in 19 cases, intracerebral hematoma in 4 cases and active hydrocephaly in 5 cases.

Seventy-four measurements of CBF were taken in these 50 patients by the Xenon 133 inhalation method perfected by Obrišt and Risberg, using a 32-detector multiprobe system (16 per hemisphere). This method is completely atraumatic and reproducible. The test began with a closed-circuit inhalation of a mixture of air, oxygen and Xenon 133 dosed at 1.5 to 2.5 millicuries per liter (i.e., 12 to 15 millicuries per patient per test). The inhalation was stopped after one minute, and the patient breathed normal room atmosphere. Next, cerebral and pulmonary radioactivity curves were recorded over a 10-minute period; a capnograph continuously measured alveolar pCO2. Two parameters were calculated from the decreasing curves:

1) $F_1$ in ml/100g/min. which is an index of the cortical flow (bicompartmental model). This value ranges from 70 to 80 ml/100g/min. in the normal subject at rest and in the absence of all physical or sensorial stimulation.

2) I.S.I. (Initial Slope Index), calculated between the 2nd and 3rd minute of the clearance curve where compartmental instability is present (monocompartmental model). Normal value ranges from 40 to 50.

Focal oligemia was considered present when local-
ized CBF decreased by more than 15% (compared with mean hemispheric flow) in at least 3 adjacent detectors. At the time of each CBF measurement, clinical grade, pCO2 and mean arterial pressure (MAP) were recorded. In 44 out of 50 patients, the initial CBF measurement was performed within the first 12 days following the bleeding.

Surgical clipping of the aneurysm was performed on 27 patients. The remaining subjects did not undergo surgery, either because they presented no arterial malformation (11 cases) or because their condition was felt to be too serious (12 cases).

The usual statistical methods were used, notably variance analysis, the Student t test and the \( \chi^2 \) test. Results with error risk less than 5% were considered significant.

### Results

1. **Correlations with Cerebral Blood Flow (table 1)**

   The 74 CBF values were correlated with the clinical grade of the patients at the time of measurement: mean CBF value was significantly lower in grade IV patients, whereas there was no difference between grade I-II and III patients. This decrease in CBF was not explained by modification in pCO2 or MAP nor by age difference. Focal oligemia occurred more often in those grade I-II and III patients with no focal neurological symptoms, localized hypoperfusion was explained by modification in pCO2 or MAP nor by age difference.

   Focal oligemia occurred more often in those having poor outcome (66%) recovered with no disability, whereas 74% of those having poor outcome (disability and deaths) were in the grade IV group.

### Table 1: Correlation Between Clinical Grade and CBF Values (74 Measurements Were Made in 50 Patients)

<table>
<thead>
<tr>
<th>Clinical grade</th>
<th>n</th>
<th>Age (years)</th>
<th>pCO2 (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>Oligemic focus (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>35</td>
<td>47.2±12.3†</td>
<td>38.2±6.6</td>
<td>32.3</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>46.1±13.6</td>
<td>38.8±12.3</td>
<td>31.8±12.2</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>53.1±11</td>
<td>30.3±7.9</td>
<td>30.4±3.2</td>
<td>0</td>
</tr>
<tr>
<td>Statistical test</td>
<td></td>
<td>F = 0.79</td>
<td>F = 6.65</td>
<td>F = 5.20</td>
<td>( \chi^2 = 11.76 )</td>
</tr>
</tbody>
</table>

2. **Influence of Patients' Age (table 2)**

   The patients' age influenced CBF values: considering only the first CBF measurement performed on each patient, it was noted that mean CBF was lower in subjects aged 50 or over as compared to younger people. The correlation coefficient between age and first CBF measurement was \( -0.37 \) for Fl (\( p < 0.01 \)) and \( -0.36 \) for ISI (\( p < 0.05 \)). However, it was not possible in this study to correlate the patients' age with the other parameters, particularly with clinical grade, focal oligemia or vasospasm.

### Table 2: Influence of Patients' Age on Clinical, Hemodynamic and Angiographic Parameters

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>Clinical grade</th>
<th>First rCBF</th>
<th>pCO2 (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>Oligemic focus</th>
<th>Vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>16</td>
<td>70.5±18.1†</td>
<td>41.5±11.8</td>
<td>32.1±2.9</td>
<td>98.7±10.3</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>III</td>
<td>16</td>
<td>60.9±11.6</td>
<td>36.3±5.8</td>
<td>32.2±8.9</td>
<td>101.8±11.2</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>60.9±11.6</td>
<td>36.3±5.8</td>
<td>32.2±8.9</td>
<td>101.8±11.2</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Statistical test</td>
<td></td>
<td>( \chi^2 = 1.60 )</td>
<td>t = 2.24</td>
<td>t = 1.98</td>
<td>t = 0.14</td>
<td>( \chi^2 = 0 )</td>
<td></td>
</tr>
</tbody>
</table>

†Mean ± SD. NS = non-significant.
were initially classified in grades I–II and III; moreover the 7 grade IV patients were equally divided among the 3 outcome groups.

On the other hand, initial CBF was greater in those patients having good recovery compared with those either suffering disabilities or dying (fig. 1). Mean values were significantly different for F1, which represented cortical flow. The same tendency, although less marked, was observed for ISI. Taking the value of 60 ml/100g/min. as the cortical level for F1 and 35 as that for ISI, it appeared that below this level the risk of complications was much greater; of the 18 patients with cortical flow below this level, 12 experienced complications, and all the deaths had shown values below this critical level except one case where cortical flow was measured at 60.3 ml. Conversely, in every case where cortical flow rose above 70 ml. outcome was good.

Focal oligemia occurred more frequently in cases with poor outcome than in those with good recovery, whereas the same type of comparison was not significant for vasospasm.

Figure 2 compared the prognostic values of clinical grade and CBF as evaluated in the first days of illness: mean cortical flow measurements were above 70/ml/ 100g/min. in those patients having favorable outcome, regardless of clinical state at time of measurement; conversely, mean cortical flow measured around 55 ml/100g/min. in those subjects who experienced complications or who died, regardless of classification in group I–II or III–IV.

4. Correlation with the Outcome of the 27 Surgical Patients (table 4)

For statistical reasons, the 27 surgical patients were divided into 2 groups, one with good recovery (19 cases), the other having postoperative complications (8 cases including 2 deaths). Neither age, clinical conditions, or absence or presence of vasospasm correlated significantly with outcome. However, marked decrease of initial cortical CBF was noted in those subjects experiencing complications. Similarly, focal oligemia occurred more frequently in this group than in those patients with uncomplicated postoperative evolution.

Discussion

As many other authors3, 7, 9, 13 have found, a certain correlation was observed between CBF values and the clinical state of patients: those with both alteration of consciousness and motor deficit showed a mean CBF decrease of 30% compared with the others. However, it seemed more valuable to emphasize the discordances which may exist between clinical and hemodynamic parameters: among grade I–II patients, certain subjects showed abnormally low CBF values: 31% had a CBF value less than 60 ml/100g/min. Conversely, 57% of grade III or IV patients had results above this critical level. It would appear that the study of cerebral hemodynamics in these patients could furnish additional results and particularly, as Ferguson has noted,3 such investigation could permit detecting those risk-prone subjects with insufficient cerebral perfusion whose clinical condition gave no indication of same.

Analysis of regional CBF can also provide valuable information: each of the 7 patients with localized clinical symptoms presented a concordant ischemic or oligemic territory. The advantage of this type of atraumatic measurement is that of following the evolution of such focal ischemic and comparing it with the patient’s clinical outcome. However, discordances could also have existed between clinical and hemodynamic re-

### Table 3 Correlations Between the 50 Patients' Outcome and Clinical, Angiographic and Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Age (years)</th>
<th>Clinical grade</th>
<th>Vasospasm</th>
<th>First rCBF</th>
<th>Oligemic focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>21</td>
<td>46.5 ± 12.7t</td>
<td>I–II III IV</td>
<td>0 +</td>
<td>71.9 ± 16</td>
<td>41 ± 11.2</td>
</tr>
<tr>
<td>Disability</td>
<td>23</td>
<td>50.2 ± 12.5</td>
<td>8 3 2</td>
<td>7 6</td>
<td>52.8 ± 8.4</td>
<td>36.9 ± 4.3</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>49.3 ± 12.1</td>
<td>2 1 3</td>
<td>2 4</td>
<td>50.1 ± 8</td>
<td>32.6 ± 4.4</td>
</tr>
<tr>
<td>Statistical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>test</td>
<td>F = 0.45</td>
<td>NS</td>
<td>x² = 8.14</td>
<td>x² = 3.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05  **p < 0.01

### Table 4 Correlations Between the 27 Surgical Patients' Outcome and Clinical, Angiographic and Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Age (years)</th>
<th>Clinical grade</th>
<th>Vasospasm</th>
<th>CBF (F1) (ml/100 g/min)</th>
<th>Oligemic focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>19</td>
<td>47.4 ± 13.2t</td>
<td>10 9</td>
<td>12 7</td>
<td>68.8 ± 11.6</td>
<td>15 4</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>8</td>
<td>51.6 ± 11</td>
<td>5 3</td>
<td>6 2</td>
<td>52.7 ± 8.6</td>
<td>1 7</td>
</tr>
<tr>
<td>Statistical</td>
<td></td>
<td>t = 0.80</td>
<td>x² = 0.22</td>
<td>x² = 0.36</td>
<td>t = 3.54</td>
<td>x² = 10.30</td>
</tr>
<tr>
<td>test</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

*p < 0.05  **p < 0.01

### Notes

1 Mean ± SD.
2 NS = not significant.
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CEREAL BLOOD FLOW and OUTCOME

FIGURE 1. Initial cerebral blood flow values for the 50 patients in terms of their outcome. F1 represents cortical flow. ISI is an index of mean flow.

Results: thus, in 30% of the grade I–II patients and 57% of those in grade III, the first CBF measurement showed clinically silent focal oligemia. In 4 patients this oligemic focus was seen a few days before the concordant clinical deficit appeared. An example illustrating this is given in figure 3. The existence of such clinically silent oligemic foci could explain ischemic strokes following arteriography or surgery in patients showing no clinical or arteriographic symptoms of high risk.

Meyer et coll. have recently stressed the influence of patients' age: they reported decreased CBF and less favorable outcome in subjects over 50. Similarly, the present study established an inverse correlation between age and blood flow. But unlike the work of the former authors, this study does not emphasize relation between patients' age and their outcome (Table III): subjects 50 years or older did not evolve in a significantly different way than the others. It may thus be concluded in this sample that decreased CBF in those subjects with poor outcome was not a function of more advanced age.

Most of the earlier studies establish a relationship between spasm and decreased CBF. The present study also revealed decreased mean CBF in subjects with spasm, but it was not possible to correlate this decrease with spasm intensity. Nevertheless, having excluded comatose patients from this study, only three cases of severe, extensive spasm were observed. As well, there was non systematic correlation between spasm seen by angiography and focal oligemia revealed through hemodynamic examination: these two methods do not explore the same vascular territory.

FIGURE 2. Comparative prognostic value of clinical grade and initial CBF measurements evaluated in the early days following meningeal hemorrhage (mean 9.7 ± 9.6 days).

FIGURE 3. A 56-year-old woman. Aneurysm of left middle cerebral artery (MCA) bifurcation. Arteriography performed on the 6th day showed no spasm. At the time of CBF measurement on the 10th day, the patient was in grade II, showing neither confusion nor deficit. This flow reading revealed major focal oligemia in the left MCA territory. Five days later, this patient became aphasic. Surgery took place on the 33rd day once mean CBF had returned to a normal value. Post-operative evolution was uncomplicated, but the patient retained aphasic deficit.
angiography shows mainly the basal and cortical arteries; Xenon 133 inhalation measures tissue perfusion, i.e. distal circulation. It is known that the narrowing of arterial lumen must be greater than 80% before distal circulation is affected. That is why angiographic vasospasm and focal ischemia may be dissociated, and why angiographic results do not provide an exact picture of tissue perfusion and consequently, of the risk of ischemia.

Finally, the essential focus of this study remains patients' outcome and the search for prognostic factors. It was observed that neither the patients' age, nor the presence of vasospasm, nor the extent of bleeding, nor the location of the aneurysm seemed to be determinant in patients' evolution (table 3). Nor was significant correlation found between initial clinical grade and outcome. It is not to be inferred, nonetheless, that clinical state has no predictive value, particularly for surgical results. To do so would be to oppose well-established ideas and daily experience. Like most other medical-surgical teams, ours does not consider operable those patients with alteration of consciousness or significant neurological deficit. Spontaneous improvement must occur before surgery is indicated. Nonetheless, it must be stated that, in this study, a significant correlation appeared between CBF measured in the first two weeks of illness and patient's outcome on leaving hospital (fig. 1). Such a correlation was not evident with initial clinical condition at the time of CBF measurement (fig. 2). This observation stands when considering solely the 27 patients later undergoing surgery (table 4).

The prognostic value of cerebral hemodynamic measurements in subarachnoid hemorrhage has been suggested by several authors. The studies record lower CBF values in those subjects having poor outcome. The decrease falls between 25 and 40% depending on the study, absolute values varying widely according to the method of CBF measurement. Ishii by intracarotid method, and Meyer et coll. by inhalation method, place the critical level at 30 ml/100g/min.; this value corresponding to mean flow rather than cortical flow. Our study seemed to indicate the critical level as 60 ml/100g/min. for cortical flow and 35 for flow, as evaluated by ISI.

This study thus confirm the significant prognostic value of CBF measurement in subarachnoid hemorrhage. Thanks to its atraumatic nature, measurement by inhalation can be repeatedly performed on the same patient with no ill effect. The approach we presently adopt in cases of spontaneous subarachnoid hemorrhage is performing the first CBF measurement as soon as possible. Mean cortical flow values less than 60 ml/100g/min. and/or focal oligemia temporarily contra-indicate surgery. In these conditions, we prefer delaying angiography and repeating CBF measurements until hemodynamic and clinical improvement safety permit further investigation.

References

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