Regional cerebral blood flow in patients with ruptured intracranial aneurysms

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Eighty-five studies of regional cerebral blood flow (rCBF) were performed on 49 patients with ruptured intracranial aneurysms. The changes in rCBF were analyzed under various pathophysiological conditions. The degree of flow abnormalities correlated well with the clinical severity of neurological deficits. All of the patients with diffuse vasospasm of severe grade, to less than half of their control value, showed focal areas of decreased flow below 30 ml/100 gm/min, in addition to a reduction in mean CBF. The relief or disappearance of vasospasm in angiograms was followed by the increase of rCBF in the ischemic focus and mean CBF. Marked reduction in rCBF was found in patients with intracerebral hematoma and ventricular dilatation. Impaired CO₂ response and autoregulation were found in patients with severe neurological deficits, a severe degree of vasospasm and marked depression of mean CBF. In this series direct operation was delayed in patients with impaired vascular reactivity as well as marked decrease of mean CBF below 30 ml/100 gm/min; good clinical results were obtained in these patients.

KEY WORDS • regional cerebral blood flow • subarachnoid hemorrhage • vasospasm • intracranial aneurysm • intracerebral hematoma • ventricular dilatation

Clinical Materials and Methods

This series comprises 49 patients of whom 32 were male and 17 female. Their ages ranged from 30 to 71 years, with an average of 49 years. Twelve of the 49 patients had multiple aneurysms. The sites of the ruptured aneurysms were as follows: 15 were associated with the internal carotid artery (ICA), 16 with the anterior communicating, two with the anterior cerebral, 15 with the middle cerebral, and one with the basilar artery. Surgical clipping of the aneurysms under the operating microscope was performed on 46 patients. The remaining three patients had no surgical intervention; one died from rebleeding before surgery could be attempted, and the other two had severe neurological deficits.

A total of 85 rCBF measurements were carried out, with each patient having one to five recordings. Measurement of rCBF was by the intra-arterial xenon-133 (¹³³Xe) injection method. The procedure was carried out as follows: The common carotid artery was punctured and a small catheter was passed into the ICA. Correct placement of the catheter was verified by injection of contrast medium and then serial angiography of the ICA was performed. About
TABLE 1
Average of 85 rCBF measurements in 49 patients*

<table>
<thead>
<tr>
<th>Clinical Grade</th>
<th>No. of Measurements</th>
<th>rCBF (ml/100 gm/min)</th>
<th>PaCO₂ (mm Hg)</th>
<th>MABP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>36</td>
<td>41.6 ± 7.2</td>
<td>40.5 ± 4.5</td>
<td>103.7 ± 20.5</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td>35.9 ± 7.2</td>
<td>41.6 ± 3.8</td>
<td>104.2 ± 15.7</td>
</tr>
<tr>
<td>IV</td>
<td>21</td>
<td>26.7 ± 5.3</td>
<td>39.9 ± 5.8</td>
<td>108.6 ± 22.6</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation. rCBF = regional cerebral blood flow; PaCO₂ = arterial CO₂ pressure; MABP = mean arterial blood pressure.

40 minutes after angiography, 3 to 4 mCi of ¹³³Xe dissolved in 5 ml of saline was rapidly injected into the artery. The gamma activity clearance rates were monitored by means of a cerebrograph.* This system consists of 32 small collimated NaI scintillation detectors; pulses from each detector are displayed logarithmically via individual ratemeters and a multiplexer on an oscilloscope screen. Calculations of rCBF were made using a microcomputer system† programmed for calculating the rCBF₀ initial with initial slope analysis, and the rCBF₀ with stochastic analysis. The rCBF₀ value was used during the resting-state measurements, and the rCBF₀ initial value was used when autoregulation or response to CO₂ was examined. The mean value of rCBF₀ was 49.5 ± 5.0 ml/100 gm/min in four patients with no neurological deficits and no abnormal findings on computerized tomography (CT). We have adopted a variation in rCBF₀ of less than 20% from mean CBF as an indication of the presence of focal ischemia, and regions were described as abnormal only if changes were present in two or more adjacent detectors.

In most patients, CO₂ response was measured by repeating CBF studies during inhalation of 5% CO₂ in air or hyperventilation. In selected cases, autoregulation of CBF was tested by lowering the ICA blood pressure by tilting the patient in a head-up position. For this measurement, rCBF₀ initial values were used, corrected for differences in CO₂ pressure by 4% change in flow per mm Hg of CO₂ pressure. A variation in rCBF₀ initial of ± 20% was adopted as an indication of the presence of abnormal CO₂ response and autoregulation. All rCBF measurements included monitoring blood pressure and arterial CO₂ pressure through the ICA's.

Patients were categorized according to their neurological status at the time of rCBF measurements, which was graded by the classification of Hunt and Hess. However, those grades were not influenced by the possible presence of serious systemic disease or severe vasospasm seen on angiograms.

The extent of vasospasm was classified into one of three types: diffuse (narrowing of intra-arterial diameter over 2 cm lengths), multi-local (multiple, localized narrowing), and local (single, localized narrowing). The diffuse type of vasospasm was further divided into two grades of severity: vasospasm reducing the caliber of an artery by more than 50% was defined as severe (diffuse-severe), while mild vasospasm represented reduction in the caliber of 25% to 50% (diffuse-mild). For an indicator of objective measure of vasospasm, a ratio between the diameter of the arteries at C₁-₂, M₁, A₂ to the diameter of the canalicular portion (C₅) of the ICA was calculated from the 32 normal angiograms. The ratio in 32 measurements was C₁-₂/C₅ = 0.755 ± 0.051, M₁/C₅ = 0.608 ± 0.065, A₂/C₅ = 0.409 ± 0.051. We used 50% or 75% of the normal ratio as measurement controls. Diffuse vasospasm which was found at the peripheral or smaller branches was classified as "peripheral."

Within 3 days before or after the rCBF measurements, all 77 CT scans‡ were performed, and the results of rCBF were compared with those of serial angiography, CT scanning, and clinical grades.

**Results**

Clinical Grade and rCBF

The degree of reduction in mean CBF and occurrence of focal ischemia correlated well with the clinical grade of neurological deficits (Table 1 and Fig. 1). Patients with more severe neurological deficits in general had a more marked depression of mean CBF: 41.6 ± 7.2 ml/100 gm/min for 36 recordings in Grade I and II patients, 35.9 ± 7.2 ml/100 gm/min for 28 recordings in Grade III patients, and 26.7 ± 5.3 ml/100 gm/min for 21 recordings in Grade IV patients. Figure 1 shows the relationship between clinical

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*Cerebrograph Model rCBF-322, manufactured by Meditronic A/S, 9560 Hadsund, Denmark.
†Microcomputer system, cerebrograph equipped with rCBF microcomputer, manufactured by Meditronic A/S, 9560 Hadsund, Denmark.
‡Scans were performed with an EMI 1000 or 1010 scanner, manufactured by EMI Ltd., 20 Manchester Square, London W1A 1ES, England.
Cerebral blood flow with ruptured aneurysms

FIG. 1. Relationship between cerebral blood flow (CBF) and clinical grade (Hunt and Hess classification). Open circles indicate the values of mean CBF. Bars represent the values of rCBF in the ischemic foci. Open circles without a bar indicate cases with no ischemic focus. The cases with hydrocephalus are shown by asterisks.

grades and results of 77 rCBF measurements performed within 3 days before or after CT scanning. Ischemic foci occurred in 13 of 33 measurements in Grade I and II patients, 16 of 25 in Grade III patients, and in 18 of 19 in Grade IV patients. None of the Grade I and II patients without ischemic foci showed abnormal CT findings at the time of rCBF measurements. Most of the Grade IV patients showed not only marked decrease of mean CBF below 30 ml/100 gm/min, but also marked ischemic foci, with rCBF below 20 ml/100 gm/min.

Vasospasm and rCBF

The relationship of occurrences of focal ischemia, a low-density area on CT scanning, and vasospasm is shown in Figs. 2, 3, and 4 for the patients in whom rCBF measurements were performed within 30 days after the onset of symptoms, and in whom no intracerebral hematoma was found by CT. In 12 patients with SAH, but without vasospasm, the value of mean CBF was 41.7 ± 6.9 ml/100 gm/min, and focal ischemia in rCBF occurred in two of 12 measurements. Three patients with local vasospasm showed no focal ischemia in rCBF, while focal ischemia occurred in 11 of 15 patients with multi-local vasospasm, seven of 10 patients with diffuse-mild vasospasm, and in all six patients with diffuse-severe vasospasm. In general, patients with the more severe degrees of vasospasm demonstrated increased occurrence of focal ischemia in the regions supplied by the involved arteries (Fig. 2). All of the patients with diffuse-severe vasospasm showed focal areas of

FIG. 2. Relationship of occurrence of focal ischemia, mean cerebral blood flow (CBF), and angiospasm in patients in whom regional CBF measurements were performed within 30 days after the onset, and intracerebral hematomas were not found on computerized tomography. The types of angiospasm are indicated as follows: dotted circle = diffuse-severe type, black circle = diffuse-mild type, white circle = peripheral type, triangle = multi-local type, square = local type, cross = no angiospasm.
significantly decreased flow below 30 ml/100 gm/min, in addition to a diffuse reduction in rCBF. However, patients with other types of vasospasm showed various degrees of reduction in the ischemic foci at the time of rCBF measurements, so we could not find apparent correlations between the type of vasospasm and reduction in rCBF (Fig. 3). The patients with low-density areas on CT scanning showed more depressed values of mean CBF than patients without low-density areas (32.1 ± 5.8 and 39.4 ± 7.7 ml/100 gm/min, respectively), but there was little difference in rCBF of the ischemic foci between both groups (Fig. 4).

**Intracerebral Hematoma and rCBF**

Nineteen rCBF measurements were performed on nine patients with intracerebral hematoma (Fig. 6). Most patients who exhibited a large intracerebral hematoma showed severe neurological deficits, focal decreased flow below 30 ml/100 gm/min corresponding to the area of hematoma, and generalized reduction in rCBF. Focal ischemia was found in all eight measurements in patients with intracerebral hematoma demonstrated by CT, and in seven of 11 measurements for patients in whom the hematoma had been removed or absorbed. There was little difference, however, in mean CBF and rCBF of the ischemic foci between both groups. These findings suggested that reduction in CBF continued for a long time, even after the intracerebral hematoma had disappeared.

**Ventricular Dilatation and rCBF**

Fourteen rCBF measurements were carried out in nine patients who showed marked ventricular dilatation on CT scanning, and in whom shunt operations had not then been performed (Fig. 1, asterisks). All these patients, with the exception of one with marked ventricular dilatation, had severe neurological deficits and showed marked reduction in mean CBF below 30 ml/100 gm/min. The rCBF value in the ischemic foci was below 20 ml/100 gm/min in nine of the 14 measurements.

**Vascular Reactivity**

The response to CO₂ was examined in 65 instances. Impaired response occurred in only five of 30 patients in Grades I and II, but in 19 of 25 patients in Grade III, and seven of 10 patients in Grade IV (Table 2). Twenty of 31 measurements that showed impaired response were found to be focal. In general, occurrence of impaired response was well correlated with the presence of neurological deficits. Patients with marked depression of mean CBF below 35 ml/100 gm/min showed impaired CO₂ response in 22 of 27 measurements, while patients without marked depression of mean CBF showed impairment in nine of 38 measurements (Table 3). Table 4 shows the relationship of CO₂ response to vasospasm for the patients in whom rCBF measurements were performed within 30 days after the onset of symptoms, and in whom in-
Cerebral blood flow with ruptured aneurysms

Fig. 5. Changes in mean cerebral blood flow (CBF) for each patient with angiospasm, in whom regional CBF measurements were performed more than twice. The relief from angiospasm was followed by the increase of regional CBF in the ischemic focus and mean CBF. The values of mean CBF are indicated by the symbols. P indicates the case with angiospasm of peripheral type.

Intracerebral Hematoma

Fig. 6. Relationship between cerebral blood flow (CBF) and intracerebral hematoma. The symbols are defined in Fig. 1. Whether intracerebral hematoma is seen on computerized tomography or has been removed or absorbed is indicated by + or −.

Intracerebral Hematoma was not found on CT. The correlation between severe degrees of vasospasm and the occurrence of CO₂ response was high. Impaired response was found in all four patients with diffuse-severe vasospasm.

Autoregulation was examined in only seven measurements, and had the same correlation of disturbance as seen in CO₂ response.

Clinical Results and Preoperative Mean CBF

Thirty-nine patients in whom rCBF measurements were performed preoperatively were followed after discharge. Their results were divided into four categories, according to their neurological condition, based on examinations made 3 months to 2 years after operation, as follows:

Excellent: no neurological deficit is demonstrable
Good: minimal deficit is demonstrable, but the patient has fully returned to his former employment
Fair: moderate neurological deficit is demonstrable, and the patient is capable of self-care in his daily activity
Poor: severe neurological deficit is demonstrable, and the patient is not capable of self-care.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Relationship of CO₂ response and autoregulation to clinical grade</th>
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<tbody>
<tr>
<td>Grade</td>
<td>Disturbance of CO₂ Response</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>I &amp; II</td>
<td>25</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Relationship of CO₂ response and autoregulation to mean cerebral blood flow (CBF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CBF (ml/100 gm/min)</td>
<td>Disturbance of CO₂ Response</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>≥ 40</td>
<td>24</td>
</tr>
<tr>
<td>36–39</td>
<td>5</td>
</tr>
<tr>
<td>30–35</td>
<td>3</td>
</tr>
<tr>
<td>≤ 29</td>
<td>2</td>
</tr>
</tbody>
</table>
The relationship of the results of these patients to mean hemispheric values of rCBF is shown in Table 5. In 26 patients with excellent results and six patients with good results, the mean CBF values, which were measured just before the operation, were more than 30 ml/100 gm/min; whereas all four patients with poor results and two of three patients with fair results showed marked reduction in mean CBF to values below 30 ml/100 gm/min.

Discussion

With the intra-arterial $^{133}$Xe injection method using 32 detectors, it is possible to detect focal flow abnormalities. In the literature, we found no criteria for determining regional differences in CBF. Hjedt-Rasmussen, et al.,14 and Paulson, et al.,18 considered a difference of 15% of the mean CBF as significant. Jaffe, et al.,11 McHenry, et al.,16 and Fieschi and Rosiers6 set the limit at 20%, although the detectors they used were of a different type. Based on these reports, we used a limit of 20% in this analysis to identify regions with focal flow disturbances. The same value was used to test CO$_2$ response, because for practical purposes the rCBF is usually increased by 20% or more in normal individuals breathing 5% CO$_2$ in air.6

Over the years a number of investigators have measured various aspects of CBF in patients with SAH due to ruptured intracranial aneurysm.1,4,6,7,10,12,14,20,24,29 We have previously reported our initial data10 which were in accord with the observations of other investigators that SAH caused a diffuse reduction in rCBF, and the degree of reduction correlated well with the clinical grade of neurological deficits. Also, in this series the degree of hemispheric flow abnormalities and the occurrence of focal ischemia, which was located in the regions where the abnormal CT findings existed, correlated well with the clinical grade of neurological deficits. It must be stressed that most of the Grade IV patients showed marked decrease of mean CBF, which was below 30 ml/100 gm/min. Furthermore, these patients also had marked ischemic foci, where rCBF was below 20 ml/100 gm/min.

Although there are various opinions in regard to the clinical significance of vasospasm, there is no room for doubt that vasospasm is one of the complications that contribute most importantly to the morbidity and mortality of patients with ruptured intracranial aneurysm. It is well recognized that narrowing of the vascular lumen can result in distal ischemia or infarction. Heilbrun, et al.,7 carried out rCBF measurements on 10 patients and found that all five who exhibited vasospasm had areas of focal ischemia which roughly corresponded to the region supplied by the involved artery. They further noted that high blood pressure maintained both by flow through narrowed arteries and flow through collaterals was a crucial factor in the outcome. Simeone12 produced experimental vasospasm in monkeys and found that at least 50% reduction in vessel caliber was necessary to drop CBF to 60%, or less than control levels. Weir and Petruk,19,26 also examined experimental vasospasm and reported that the reduction of flow following SAH was in the order of 50 to 30 ml/100 gm/min. Monkeys that displayed a reduction in rCBF exhibited a mean vessel caliber decrease of 35% throughout the acute period of observation, while monkeys with no decrease in rCBF had a mean vessel caliber decrease of 26%. This difference in vessel caliber was not statistically significant. Furthermore, monkeys in which CBF was reduced significantly displayed severe neurological abnormality. The conclusion of the investigators was that an impairment of neurological status appeared to be more directly related to the reduction of rCBF than to change in the caliber of angiographically observable arteries. Mathew, et al.,14 reported that, when vasospasm was relieved by phenoxybenzamine, rCBF did not increase although regional cerebral blood volume did; they suggested that other factors might be more important for the reduction of rCBF, such as cerebral edema and communicating hydrocephalus.

In our previous report,10 we analyzed the changes in mean CBF in patients with vasospasm. Vasospasm was often associated with a reduction in mean CBF. However, reduction in mean CBF occurred even in the patients in the best clinical condition (Grades I and II).

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**TABLE 5**

<table>
<thead>
<tr>
<th>Postop Results</th>
<th>No. of Cases</th>
<th>rCBF* (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>excellent</td>
<td>26</td>
<td>41.8 ± 7.2</td>
</tr>
<tr>
<td>good</td>
<td>6</td>
<td>39.7 ± 5.9</td>
</tr>
<tr>
<td>fair</td>
<td>3</td>
<td>31.0 ± 5.7</td>
</tr>
<tr>
<td>poor</td>
<td>4</td>
<td>25.0 ± 3.1</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation.
without vasospasm, and vasospasm was not necessarily associated with depressed flow and neurological deficits. Therefore, it was suggested that vasospasm alone was not likely to be responsible for the reduction in mean CBF. In this series, it was apparent that most of the patients with vasospasm showed focal ischemia in the regions supplied by the involved arteries. All of the patients with diffuse vasospasm of severe grade, to less than half of their control value, showed focal areas of decreased flow below 30 ml/100 gm/min in addition to a reduction in mean CBF. However, the patients with other types of vasospasm showed various degrees of reduction in the ischemic foci just at the time of rCBF measurements. The patients with low-density areas on CT showed more depressed values of mean CBF than those without low-density areas, but unexpectedly there was little difference in rCBF in the ischemic foci between both groups. Furthermore, the low-density areas which were found in patients with severe vasospasm did not always persist for a long time. This must be due to the pathological basis of low-density areas, which could contain cerebral edema as well as necrosis.\(^3\)

It would be interesting and important to know the critical flow for adequate cerebral function, but various factors, such as degree of arterial narrowing, extent of the process, duration of involvement, perfusion pressure, intracranial pressure, and disturbance of cerebral metabolism, have to be taken into consideration. Several studies concerning ischemic tolerance of cerebral tissue were performed during carotid endarterectomy. Boysen\(^2\) observed postoperative aggravation of neurological deficits in five patients in whom rCBF was at or below 30 ml/100 gm/min during the period of carotid clamping. Trojaborg and Boysen\(^2\) found that flattening of the electroencephalogram (EEG) occurred when the rCBF fell to between 11 and 19 ml/100 gm/min, and slowing was seen when the rCBF fell to between 16 and 22 ml/100 gm/min. Sharbrough, \textit{et al.},\(^7\) reported that no EEG change was seen with the flow above 30 ml/100 gm/min, only minor changes were seen with a flow between 18 and 30 ml/100 gm/min, and changes invariably occurred with a flow below 17 ml/100 gm/min. From the data mentioned above, Sundt\(^2\) hypothesized that, in patients with vasospasm, mean CBF above 30 ml/100 gm/min could be tolerated without neurological change; reduction below this level could lead to neurological deterioration, and major neurological alterations could occur when mean CBF fell below 20 ml/100 gm/min. However, Sundt called attention to a major problem, the “look-through” phenomenon, when measuring rCBF by the intraarterial \(^{133}\)Xe injection method. It is not possible with current techniques to prevent the contamination of measurements from an ischemic zone with counts actually coming from deeper non-ischemic regions. Similar problems exist in recording rCBF in patients with vasospasm, because of a failure of the indicator to reach the area under investigation. He concluded that measurements of rCBF during carotid endarterectomy are free from the “look-through” artifact. However, the critical levels of our series, mean CBF, 30 ml/100 gm/min and rCBF, 20 ml/100 gm/min, closely resembled the levels that were measured during carotid endarterectomy.

It is apparent that our patients with intracerebral hematoma and/or hydrocephalus had severe neurological deficits. Measurement of rCBF showed focally decreased flow below 30 ml/100 gm/min corresponding to the area of hematoma, and generalized reduction in rCBF. Fourteen studies in patients with hydrocephalus showed marked reduction in mean CBF below 30 ml/100 gm/min. The rCBF value in the area of hematoma and vasospasm decreased more markedly to below 20 ml/100 gm/min when accompanied by ventricular dilatation. It appears from the present study that evacuation of the hematoma, relief of ventricular dilatation, and control of brain edema might increase rCBF, and consequently result in improvement of neurological deficits and a good clinical prognosis.

A major question that remains unanswered is the timing of operation, although the ideal method for managing patients with ruptured intracranial aneurysms should be the one that provides immediate surgery to eliminate the chance of rebleeding. It is essential in solving this problem and producing a better form of therapy to know the various pathophysiological conditions following rupture of an intracranial aneurysm. It is apparent from the present study that a mean CBF value of more than 30 ml/100 gm/min, measured just before the operation, resulted in good clinical prognosis. Analysis of the vascular reactivity which involves capability for autoregulation and sensitivity to CO\(_2\) might be important in determining the optimum time for surgical intervention, which requires manipulation of the aneurysm-bearing arteries. In the present study, impaired CO\(_2\) response and autoregulation were found in patients with severe neurological deficits, a severe degree of vasospasm, and marked depression of mean CBF. Heilbrun, \textit{et al.},\(^7\) demonstrated global impairment of autoregulation in patients who had deteriorated following SAH, and implied that it might be worthwhile to base delay of surgical intervention on restoration of autoregulation as well as clinical improvement. In this series, we delayed direct operation on the patient with impaired vascular reactivity as well as marked decrease of CBF, and obtained a good clinical result.

\textbf{Acknowledgments}

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References


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