Abnormal Hemispheric Blood Flow and Metabolism Despite Normal Angiograms in Patients with Stroke

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Abstract:
Hemispheric blood flow (HBF) and metabolism were measured using the intracarotid injection of hydrogen-saturated saline in a group of patients with unilateral hemispheric infarction, some of whom had normal angiograms. Blood flow was calculated from the formula derived from the Stewart-Hamilton principle using the clearance curve of hydrogen in the cerebral transverse sinus. Hemispheric metabolic index was estimated using a newly developed formula by assuming that the distribution of hydrogen into each transverse sinus following intracarotid injection indicates the distribution of blood from each hemisphere into each transverse sinus.

HBF and oxygen metabolism on the affected side were reduced in all groups, but the reduction was greater in patients with angiographical evidence of vascular occlusion. In many patients, HBF and metabolism on the nonaffected side which angiograms showed to be normal were reduced in the acute phase.

It is apparent that by using the hydrogen bolus technique of measuring HBF and metabolism, small disturbances in cerebral circulation can be detected which are not discernible in angiograms.

Additional Key Words: internal carotid occlusion, collateral circulation, intracranial disease

In the past decade, cerebral angiography has been used extensively in the diagnosis and evaluation of patients suffering from cerebrovascular disease (CVD). Some authors have reported, however, that in 20% to 60% of their patients with occlusive CVD angiograms failed to demonstrate any abnormality, and little obvious association may exist between abnormalities demonstrated angiographically and some clinical signs. Hence, it seems important to supplement conventional neuroradiological procedures with other measurements of cerebral function such as regional blood flow and metabolism.

Important contributions to the fund of knowledge of cerebral hemodynamics have been made possible by the radioisotope injection method for measuring regional blood flow developed by Lassen, Ingvar, and associates. However, relatively little has been said in the published series of patients with CVD concerning angiographical findings in association with changes in regional cerebral blood flow. Furthermore, radioisotope methods currently employed present some theoretical disadvantages with respect to the exact geometry of the areas measured from the detectors, and because of Compton scatter regional reductions of blood flow may produce widespread artifactual reduction in CBF. Furthermore, metabolic changes have not been measured in conjunction with regional CBF using krypton 85 and xenon 133.
Bearing this in mind, we measured the hemispheric blood flow (HBF) and metabolism in patients suffering from acute or chronic CVD involving one hemisphere (completed stroke) in whom serial cerebral angiograms were also performed. As many patients as possible in whom the angiograms were normal were selected for study. In this communication, the term "normal angiogram" is used to mean there was no demonstrable stenosis or occlusion of the cerebral vessels including the internal carotid artery. Kinking and tortuosity of vessels and generally delayed circulation of the contrast media were not considered abnormal for the purposes of this study.

**Methods**

Twenty-two patients with unquestionable signs and symptoms of occlusive cerebrovascular disease were included in this series. Their ages ranged from 30 to 74 years, with a mean of 53 years. Angiograms were performed in nearly every patient prior to measurement of blood flow, and the patients were separated according to angiographical findings into two major categories (table 1). Group 1 consisted of patients in whom the angiograms were normal, and those in group 2 had abnormal angiograms. Group 2 was divided further into two subgroups. Group 2a consisted entirely of patients with occlusion or severe stenosis of one internal carotid artery, and group 2b comprised patients with disease of the intracranial vessels. No cases of early filling of the veins or angiographical "blush" were included, and patients with angiographically demonstrated combined intracranial and extracranial disease were excluded from the study.

Following intramuscular administration of atropine sulfate 0.4 mg, meperidine hydrochloride 50 mg, and hydroxyzine hydrochloride 50 mg, a catheter was inserted under fluoroscopic control into each cerebral transverse sinus via the basilic veins. Another catheter was placed into the femoral artery to obtain arterial samples. Blood from each transverse sinus and the femoral artery was pumped through cuvettes containing hydrogen, pO₂, Pco₂, and pH electrodes. Glucose, lactate, and pyruvate levels of the blood were also continuously measured using the Technicon Auto Analyzer.

The blood flow of each hemisphere was obtained using the hydrogen bolus method described in prior reports. Following the appropriate injection of a 5 to 6 ml bolus of hydrogen-saturated saline into each internal carotid artery, clearance curves were obtained from the ipsilateral transverse sinus. The formula for calculating HBF was:

\[
HBF = \frac{\int_{0}^{t_d} p(t) \, dt}{\int_{0}^{t_d} t \cdot p(t) \, dt} \times 100 \text{ (ml/100 gm brain/min)}
\]

where \(t_d\) denotes the time when hydrogen disappears from the transverse sinus blood, \(p(t)\) is the partial pressure of hydrogen at time \(t\), and \(t\) is the time when hydrogen disappears from the transverse sinus blood.

**TABLE 1**

<table>
<thead>
<tr>
<th>Angiographical findings</th>
<th>No. cases</th>
<th>Age (years)</th>
<th>HBF</th>
<th>HMI-O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Affected side (ml/100 gm brain/min)</td>
<td>Nonaffected side (ml/100 gm brain/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBF</td>
<td>HBF</td>
</tr>
<tr>
<td>Group 1: Normal</td>
<td>9</td>
<td>55 ± 12</td>
<td>36.4 ± 4.5</td>
<td>38.7 ± 4.9</td>
</tr>
<tr>
<td>Group 2: Abnormal</td>
<td>13</td>
<td>51 ± 12</td>
<td>35.8 ± 3.9</td>
<td>41.7* ± 5.6</td>
</tr>
<tr>
<td>(a) Carotid occlusive disease</td>
<td>8</td>
<td>57 ± 7</td>
<td>34.2 ± 3.0</td>
<td>41.5* ± 3.2</td>
</tr>
<tr>
<td>(b) Intracranial occlusive disease</td>
<td>5</td>
<td>42 ± 12</td>
<td>37.8 ± 4.3</td>
<td>42.1 ± 8.3</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. HMI-O₂ is not shown in groups 2a and 2b as there were too few cases for separate calculation. *Statistically significant difference from affected side.
is time after injection of the bolus. In this series, blood flow was calculated over an interval of ten minutes.\textsuperscript{16} The region measured is the area saturated with hydrogen following injection into one internal carotid artery, i.e., one hemisphere or, in cases of internal carotid occlusion, a part of a hemisphere. HBF was measured on both sides, whenever possible, by injecting hydrogen into each internal carotid artery.

Estimated hemispheric metabolism was calculated using a new formula described in detail in another report.\textsuperscript{17} Cerebral metabolism has been routinely calculated from the product of blood flow and the arteriovenous metabolic differences. However, it is well known that each internal jugular vein or transverse sinus contains blood derived from both hemispheres. Although each internal jugular vein is fairly representative of its ipsilateral hemisphere, the ratio of mixing is different in each individual. Therefore, hemispheric venous metabolic contents such as oxygen, glucose, lactate, and pyruvate were calculated using the new formula, which assumes that hydrogen distribution indicates the distribution of blood from each hemisphere into each transverse sinus:

\[
V(t) = \frac{bC_1(t) - C_3(t)}{b-1}
\]

where \( V(t) \) is hemispheric venous content of metabolite at time \( t \), and \( b \) is the ratio of partial pressure of hydrogen appearing in the contralateral transverse sinus compared to that appearing in the ipsilateral sinus after contralateral carotid injection of hydrogen. \( C_1(t) \) and \( C_3(t) \) are the concentrations of metabolites in the ipsilateral and contralateral transverse sinuses, respectively.

Hemispheric metabolic index was calculated from the product of HBF and hemispheric arteriovenous differences for oxygen (HMI-O\textsubscript{2}), glucose (HMI-G1), lactate (HMI-Lact), and pyruvate (HMI-Pyr). All of the results were analyzed using the standard \( t \) test and \( P \) value.

Differences with a possible error of 5\% or less were considered significant.

**Results**

In nine patients from a series of 22 with unquestionable signs of unilateral cerebral infarction, the angiograms showed no abnormality. All patients with normal angiograms, except one, had suffered recent cerebral infarction. The mean HBF on the affected side was 36.4 ± 4.5 ml/100 gm brain/min, and the mean index for hemispheric oxygen metabolism was 2.31 ± 0.48 ml/100 gm brain/min (table 1). HBF was decreased more markedly in 13 patients with abnormal angiograms, and reduction of HBF on the affected side in the group of patients with carotid occlusive disease tended to be more severe than in those with occlusive disease of the intracranial vessels, although the reduction in HBF on the affected side in those with normal angiograms as well as in those with extracranial or intracranial occlusive disease was not significantly different. It is of interest that the hemispheric metabolic index for oxygen in the group with abnormal angiograms was reduced more markedly than in the group with no angiographical abnormality (0.3 > \( P > 0.2 \)).

HBF on the nonaffected side was also measured and compared with that on the affected side. A decrease in both HBF and HMI-O\textsubscript{2} was also found on the nonaffected side in all groups with normal angiographical findings. HBF and HMI-O\textsubscript{2} on the nonaffected side were reduced to a greater degree in group 1, which included more acute cases than group 2.\textsuperscript{18}

Calculated HMI-G1, HMI-Lact, HMI-Pyr, and glucose:oxygen utilization ratio

**Table 2**

<table>
<thead>
<tr>
<th>Carbohydrate Metabolism in Patients with CVD</th>
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<tbody>
<tr>
<td>Angiographical findings</td>
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<tr>
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<tr>
<td></td>
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<tr>
<td>Group 1: Normal</td>
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<td></td>
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<td>Group 2: Abnormal</td>
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</table>

Values are mean ± standard deviation.

(G/O) showed no significant differences between the two hemispheres (table 2).

**Comment**

It is important to recognize that the percentage of normal versus abnormal angiograms in patients with CVD differs from one investigation to another because of the length of the interval between the onset of symptoms and the performance of the angiogram, the angiographical technique used, the type of CVD, and the criteria for definition of abnormal angiograms. However, it appears widely accepted that at least 20% of the angiograms will be normal despite a definite neurological deficit.

In this series of patients, the term “normal angiogram” is defined as one without demonstrable stenosis or occlusion of the intracranial and extracranial cerebral vessels. It has also been shown that repeated angiograms in patients with early stroke symptoms sometimes reveal complete clearing of occlusive lesions. Therefore, blood flow and metabolism measurements were performed as soon as possible after the angiographical examination.

Measurements of regional cerebral blood flow by investigators who used the radioactive inert gas indicators^8^–^11^ showed that both regional blood flow and mean hemispheric blood flow were reduced in most cases of acute stroke. The reduction in regional and hemispheric flow was greater in patients with angiographical abnormalities. The present study is in good agreement with these reports; however, in previously reported studies the mean hemispheric blood flow values in their patients with normal angiograms were only slightly reduced,^8^ while our patients with normal angiograms and hemiparesis showed more marked reduction of HBF on both the affected and nonaffected sides. Previously reported findings have also indicated that if regional flow in one zone of a hemisphere is severely reduced, there is a parallel reduction of average hemispheric flow.

The findings reported herein are the first to correlate changes in regional metabolism with angiographical observations. There was a marked reduction in oxygen metabolism in both hemispheres of patients with acute hemispheric infarction. The series is small, but there was a tendency for the oxygen metabolism to be reduced more in the infarcted hemisphere and, to a greater extent, in patients with abnormal angiograms, but these changes did not reach the level of statistical significance. Similar observations were made with regard to HMR-G1 but the series was too small to establish statistically significant differences.

It is not surprising that measurements of HBF and metabolism should show abnormalities while the angiograms are normal. Angiograms show anatomical obstructions in vessels, but reveal little about perfusion of the capillary bed. Measurements of HBF and metabolism show that despite normal angiograms, such patients have reduced blood flow and impaired metabolism but the impairment is less than in patients with abnormal angiograms. The observation that normal angiograms are observed more frequently in patients who have a good prognosis for recovery of function^2^ may also be explained on this basis.

**Acknowledgment**

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**References**

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