Bilateral Reduction of Hemispheric Blood Flow in Patients With Unilateral Cerebral Infarction

BY MASATOSHI FUJISHIMA, M.D., KENJIRO TANAKA, M.D., YO TAKEYA, M.D., AND TERUO OMAE, M.D.

Abstract: Bilateral hemispheric blood flow was determined by the intravenous RISA technique in patients with unilateral cerebral infarction. Of all 29 patients, bilateral reduction of cerebral blood flow (CBF) was demonstrated in 13, of whom hemispheric vascular resistance was significantly increased and arm-to-brain circulation time prolonged.

In these cases with bilateral subnormal CBF, blood flow on the noninfarcted side tended to increase if the patients were conscious at the time of onset, whereas it remained unchanged even 77 days following stroke if their consciousness was impaired. The already lowered blood flow on the infarcted hemisphere, however, did not increase for a relatively long period of time after the onset.

It appears that bilateral reduction of CBF in patients with unilateral infarction is primarily caused by diffuse cerebral vascular changes and some additional systemic circulatory disorder. The possibility of other factors participating is also discussed.

Additional Key Words: cerebral vascular resistance, diffuse cerebral arteriosclerosis, arm-to-brain circulation time, systemic circulatory disorder.

Transneural or transhemispheric reduction of cerebral blood flow contralateral to the infarcted hemisphere was first described by Hjøltdt-Rasmussen and Skinhøj, and also by Meyer et al. The mechanism of this phenomenon has not been fully understood, although a local metabolic depression following the unilateral hemispheric infarction is thought primarily to cause the functional depression of the contralateral hemisphere, resulting in the lowered blood flow on that side. In animal experiments on unilateral cerebral infarction, however, such a phenomenon as transneural reduction of cerebral blood flow has not been demonstrated.

In the present study, the authors selected patients with unilateral cerebral infarction having no or minor evidence of angiographical abnormalities of the brain vessels, and measured bilateral hemispheric blood flow by the RISA dilution technique to clarify the frequency with which this transhemispheric blood flow reduction occurs in these patients and what causes it.

Methods

Twenty-nine patients with unilateral hemispheric infarction, 22 males and seven females, were selected for this study. Their ages ranged from 23 to 72 years, averaging 54 years. In all patients, histories were carefully obtained and neurological examinations were performed. Twenty-two of the 29 cases were conscious and the remaining seven were mildly lethargic or semiconscious at the time of the onset, although none had disturbance of consciousness during the measurement of brain circulation.

Electrocardiography, lumbar puncture, and cerebral angiography of at least three neck vessels were performed in all patients, and electroencephalography was obtained in all but one patient. The following cases were excluded: brain stem infarction, cerebral embolism due to cardiac valvular diseases, and unilateral hemispheric infarction with more than 25% narrowing of the intracranial or extracranial vessels on the angiogram.

Cerebral blood flow (CBF) was determined by the intravenous RISA method. Two hundred microcuries of I-131 RISA were injected rapidly into the antecubital vein, and the hemispheric RISA dilution curves were obtained by NaI scintillation detectors collimated separately to each hemisphere. CBF was calculated by using the following equations:

\[
\text{CBF} = \frac{\text{CBV}}{\text{TT}} \times 60 \, (\text{ml/min})
\]

\[
\text{L/R-CBF} = \frac{\text{L/R-CBV}}{\text{L/R-TT}}
\]

\[
\text{L-CBF} = \text{CBF} \times \frac{\text{L/R-CBF}}{\text{L/R-CBF} + 1} \, (\text{ml/min})
\]

\[
\text{R-CBF} = \text{CBF} - \text{L-CBF} \, (\text{ml/min})
\]

where CBV is cerebral blood volume, and TT is mean transit time, both of which are directly measured. L/R-CBF is the ratio of the left-to-right hemispheric CBF, and L-CBF as...
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CBF on the side opposite the infarct was reduced below the normal range in 13, and was normal in three of 16 patients with subnormal flow on the infarcted side, whereas all 13 patients with normal CBF on the infarcted side had normal CBF on the noninfarcted side. Figure 1 depicts the individual values of bilateral CBF at various time intervals from the onset. Bilateral depression of CBF persisted for up to 77 days after the onset.

Figure 2 shows the percentage difference between CBF values in the infarcted and the noninfarcted hemispheres at various intervals from the onset in 16 patients with subnormal CBF on the infarcted side. In 11 of 16 patients having no impairment of consciousness, the difference increased as the time from onset elapsed, i.e., CBF on the healthy side was gradually and consistently increased toward normal, while CBF on the diseased side remained low. In five patients having impaired consciousness at onset, however, the percentage difference of CBF remained unchanged even 77 days after onset.

RELATION OF HEMISPHERIC CBF TO CLINICAL FINDINGS

Based on the CBF values, the 29 patients were divided into three subgroups: Group 1: bilaterally normal hemispheric CBF (13 cases); Group 2: subnormal CBF on the infarcted but normal CBF on the contralateral side (three cases); Group 3: bilateral subnormal hemispheric CBF (13 cases). Table 1 summarizes the relationship between CBF subgroup and each parameter.

Level of Consciousness at Onset

In Group 3, five of 13 patients (38%) had impairment of consciousness, whereas two of 13 patients (15%) in Group 1 had impaired consciousness.

Retinopathy Graded by Keith-Wagner-Koidai Classification

In Group 3, three of 12 patients (25%) had Grade II B retinopathy associated with hypertension, whereas in Group 1 only one of 13 patients (8%) had Grade II B retinopathy associated with hypertension.

Severity of Clinical Status

According to the clinical course within two months following the onset, the severity of clinical status was classified into four grades: Grade 1, recovered; Grade 2, ameliorated; Grade 3, not improved or worsened; Grade 4, died (none of the cases included in the present study).

There was no patient of Grade 3 severity in Group 1, whereas four of 13 patients (31%) were Grade 3 in Group 3.

Electroencephalogram

There were four of 12 cases (33%) in Group 3 who had moderate to severe abnormalities in EEG, whereas only one of 12 cases (8%) in Group 1 had similar
TABLE 1
Relation of Hemispheric Blood Flow to Clinical Findings

<table>
<thead>
<tr>
<th>Blood flow on infarcted side</th>
<th>Group 1 normal</th>
<th>Group 1 decreased</th>
<th>Group 2 decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow on noninfarcted side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consciousness at time of onset</td>
<td>Normal</td>
<td>Impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/13 (85%)</td>
<td>2/13 (15%)</td>
<td></td>
</tr>
<tr>
<td>Retinopathy (Keith-Wagner-Keidai grade)</td>
<td>0</td>
<td>1/13 (8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5/13 (38%)</td>
<td>1/2 (50%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>IIA</td>
<td>6/13 (46%)</td>
<td>1/2 (50%)</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>IIB</td>
<td>1/13 (8%)</td>
<td>0/2 (0%)</td>
<td>3/12 (25%)</td>
</tr>
<tr>
<td>Severity of clinical status</td>
<td>Recovered</td>
<td>Ameliorated</td>
<td>Not improved</td>
</tr>
<tr>
<td></td>
<td>7/13 (54%)</td>
<td>6/13 (46%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/3 (67%)</td>
<td>1/3 (33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5/13 (38%)</td>
<td>4/13 (31%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/13 (31%)</td>
<td>4/12 (33%)</td>
<td></td>
</tr>
<tr>
<td>Electroencephalogram</td>
<td>Normal</td>
<td>Slightly abnormal</td>
<td>Moderate-severely abnormal</td>
</tr>
<tr>
<td></td>
<td>6/12 (50%)</td>
<td>5/12 (42%)</td>
<td>1/12 (8%)</td>
</tr>
<tr>
<td></td>
<td>1/3 (33%)</td>
<td>2/3 (67%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/13 (31%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/12 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Normal</td>
<td>Dysrhythmia</td>
<td>High-R and/or ST-T change</td>
</tr>
<tr>
<td></td>
<td>3/13 (23%)</td>
<td>7/13 (54%)</td>
<td>6/13 (46%)</td>
</tr>
<tr>
<td></td>
<td>1/2 (50%)</td>
<td>0/2 (0%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td></td>
<td>4/13 (31%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

changes. In 50% of Group 1 and 25% of Group 3, the EEGs were normal.

Electrocardiogram
ECG findings were divided into three categories: (1) high voltage of QRS complex and/or ST-T changes, (2) dysrhythmias including conduction defects, and (3) normal pattern. There was no apparent difference of ECG abnormalities among three subgroups.

Mean Arterial Blood Pressure (Fig. 3)
An average MAP was almost identical among the subgroups.

Cerebrospinal Fluid Pressure (Fig. 4)
CSF pressure was normal in all of 13 patients of Group 3, whereas CSF pressure higher than 200 mm H₂O was observed in three of 13 patients of Group 1 and one of three patients in Group 2. It indicates that the lower CBF is not associated with the higher CSF pressure.

Hematocrit (Fig. 5)
Mean values of hematocrit were almost identical among the subgroups.

Arm-to-Brain Circulation Time (ABCT) (Fig. 6)
The appearance time at the brain of RISA after injection in the antecubital vein is the sum of the full pulmonary circulation time and of the partial systemic circulation time. An average ABCT was 15.9 seconds in Group 1, 19.6 seconds in Group 2, and 20 seconds in Group 3; the difference between Group 1 and Group 2 was significant (P < 0.05).

Cerebral Vascular Resistance (Fig. 7)
CVR was calculated from MAP and each hemispheric CBF. In patients of Group 3, the average CVR on the infarcted side was 31.6 mm Hg per milliliter per minute, and on the noninfarcted side 28.3 mm Hg per milliliter per minute, whereas in patients of Group 1, it was 17.1 and 16.4 mm Hg per milliliter per minute respectively. Difference between the two groups was statistically significant (P < 0.001). In patients of Group 2, CVR on the infarcted side was greater that on the contralateral side, and the average CVR was greater than that of Group 1, but smaller than that of Group 3.

Discussion
Bilateral reduction of hemispheric blood flow was observed in 13 of 29 patients (45%) with unilateral hemispheric infarction. In these cases, vascular resistance of the infarcted and noninfarcted hemispheres increased markedly, although the intracranial or extracranial arteries appeared normal or had a minor angiographical evidence of narrowing or sclerotic changes. The narrowing to less than 25% of normal diameter is not sufficient to reduce blood flow whereas more than 70% reduction in cross-sectional area of the lumen or occlusion of vessels is necessary to reduce blood flow pronouncedly.®

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In those patients conscious at onset and having bilateral reduction of CBF, the CBF contralateral to the infarcted side increased gradually and progressively toward normal value as the time elapsed after the onset. On the other hand, bilateral depression of CBF persisted for more than two months after the onset in patients having impaired consciousness of any degree at onset. From these findings, bilateral reduction of CBF could not be simply explained by the theory proposed by Meyer et al., who concluded in their series that bilateral depression of hemispheric blood flow is presumably due to transhemispheric metabolic depression following unilateral cerebral infarction.

Cerebral edema or increased intracranial pressure must be considered as another factor causing bilateral CBF reduction, although there was no evidence of cerebral edema or a CSF pressure higher than 200 mm H2O in our series. An increase in blood viscosity possibly might be another factor causing a reduction in CBF as in the case of polycythemia vera. In the present study, however, there was only one case having a hematocrit value more than 55%, above which CBF starts to decrease.

Meyer and his co-workers excluded the possibility that generalized cerebral arteriosclerosis is a cause of this phenomenon, since they reported one young patient with unilateral cerebral embolism of cardiac origin in whom hemispheric blood flow decreased bilaterally, although there was no evidence of diffuse cerebral vascular disease on the angiogram. From our experience, CBF decreased bilaterally in patients with mitral valvular diseases with or without cerebral embolism, suggesting that CBF in either
Arm-to-brain circulation time and CBF subgroups. ABCT tends to be prolonged in patients with bilateral reduction of CBF in Group 3.

Hemispheric vascular resistance and CBF subgroups. In patients of Group 3 the vascular resistance is significantly higher on both the infarcted (inf.) and noninfarcted (non-inf.) hemisphere than that in those of Groups 1 or 2.

hemisphere might be reduced in these patients prior to an embolic event.

Generalized cerebral arteriosclerosis, even though it could not be demonstrated on angiography, may be a possible cause for bilateral reduction of CBF. The calculated CVR was significantly greater on the infarcted and noninfarcted hemispheres in patients with bilateral reduction of CBF compared to those with normal CBF, suggesting that the distensibility of the intracranial resistance vessels might be diffusely impaired on either infarcted or contralateral hemispheres. Shinohara et al. demonstrated a significant reduction of hemispheric blood flow on the side of an occluded middle cerebral artery but no change on the contralateral one in the monkey. This suggests that reduction of CBF could not occur on the side contralateral to the occluded artery unless some additional factor, such as a reduction in systemic perfusion pressure, was present.

A metabolic basis for this phenomenon is proposed by other investigators. However, Høedt-Rasmussen and Skindlev described no metabolic data. Meyer et al. measured hemispheric oxygen consumption and glucose utilization in patients with unilateral infarction; both were reduced on each hemisphere. Pathways through the corpus callosum or via the brain stem route may be important, but there is no evidence for this. Substances such as serotonin or acidic metabolites such as lactate may be released from the damaged brain tissue and diffuse into the interstitial space. Intracarotid-injected or topically applied serotonin has a vasoconstricting action to the cerebral vessels, whereas endogenous lactic acid has a vasodilating action. It is unknown how long serotonin is released from infarcted tissue. There was no consistent difference in the levels of blood serotonin in cases with cerebrovascular disease and control subjects, nor any correlation between the levels of serotonin and the presence or absence of cerebral arterial spasm.

CSF lactate increases markedly in humans immediately after acute cerebral infarction and tends to return toward normal level within 15 days after onset. It seems unlikely that serotonin is released for as long as three weeks or more after onset, since Misra et al. have demonstrated that within 24 hours after acute cerebral infarction the levels of serotonin in cerebrospinal fluid were significantly high but were similar to the control value after three weeks. On the other hand, bilateral reduction of CBF lasted for two or three weeks to a maximum of 77 days in our series. Therefore, it seems unlikely that biochemical substances such as serotonin cause a decrease in CBF or the noninfarcted hemisphere.

In conclusion, it seems likely that bilateral reduction of CBF in patients with unilateral infarction is caused by a diffuse increase in cerebrovascular resistance plus some systemic circulatory disorder. It is less likely that a biochemical substance is release...
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from the damaged brain tissue to cause vasoconstriction.

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