Relationship of Serial Measurements of Cerebral Hemodynamics to Prognosis in Patients with Hypertension and Cerebrovascular Disease

BY SABURO YAMAOKA, M.D.,* YASUYUKI TAKAGI, M.D.,† TOSHIHIRO OKADA, M.D.,* AND YOSHIO SAITO, M.D.*

Abstract: Relationship of Serial Measurements of Cerebral Hemodynamics to Prognosis in Patients with Hypertension and Cerebrovascular Disease

Baseline and follow-up measurements of cerebral hemodynamics were performed in hypertensive patients by the N₂O method with a certain time interval. A tendency for some decrease in the CBF was noted, but the difference was not statistically significant.

Twelve hypertensive patients suffered from a stroke during the period of observation. The CBF values prior to the stroke varied so widely that there was no predictive value from these measurements.

The decrease in CBF in a mild case of cerebral infarction is slight and is followed by little fluctuation. The decrease in a case of moderate severity is marked but returns to normal in two to five months. Clinically severe cases of infarction and hemorrhage are also characterized by a marked decrease in CBF, but this decrease of infarcted cases may be irreversible.

A higher incidence of recurrent infarction is noted in those patients in whom recovery of CBF following a stroke is poorest. This is most apparent in those patients suffering a recurrence within one year.

ADDITIONAL KEY WORDS
postapoplectic cerebral circulation
preapoplectic cerebral circulation

Introduction

Productive life may be profoundly altered by the mental and physical changes that follow stroke. Presumably such changes of cerebral function may be reflected by alteration in cerebral hemodynamics and metabolism. In order to test this hypothesis, hypertensive patients were followed for an extended period of time to measure serial changes in cerebral hemodynamics occurring before and after the onset of stroke, e.g., a prospective study. No prospective study with such measurement has been reported previously. The authors followed the clinical course of a large number of patients with hypertension for an extended period of time, making repeated measurements of cerebral hemodynamic patterns. Eighteen patients had a stroke during the interval of observation; 12 of these had cerebral infarction and six suffered from cerebral hemorrhage. However, only 12 patients (eight infarctions and four hemorrhages) had serial measurements of hemodynamics and the rest of them had only one measurement before stroke. This paper reports data comparing changes in cerebral hemodynamic measurements obtained at various stages in the evolution of hypertension to stroke.

Methods

The study consisted of a total of 303 patients who had been seen or hospitalized at the Keiyu Hospital, Yokohama, Japan, between January, 1961 and February, 1971. One hundred fifty-seven
patients had hypertension without clinical evidence of cerebrovascular disease and 146 had definite evidence of pre-existing cerebrovascular disease.

The average age for the entire study group was 56.9 years. After initial measurements of cerebral hemodynamics, follow-up periods were from one to ten years with an average of 41 months.

Measurements of average cerebral blood flow and hemodynamics were performed in accordance with the modification of the Kety-Schmidt method developed at Keio University using a sampling technique (Aizawa). A total of 576 measurements were made. There were one to seven determinations per patient with an average of 1.9 measurements per case. In addition to measuring cerebral blood flow (CBF) (ml/100 gm brain/min), cerebral oxygen consumption (CMRO2) (ml/100 gm brain/min), cerebral vascular resistance (CVR) (mm Hg/ml/100 gm brain/min) and cerebral respiratory quotient (CRQ) were also calculated from CBF, mean arterial blood pressure (MABP) and cerebral arteriovenous difference in oxygen (A-VO2). Partial pressures of arterial and venous oxygen and carbon dioxide (PaO2, PvO2, PaCO2, PvCO2) were determined with an IL blood gas analyzer.

Results

CEREBRAL HEMODYNAMICS IN HYPERTENSION

Two separate measurements of cerebral hemodynamics were performed in accordance with the modification of the Kety-Schmidt method developed at Keio University using a sampling technique (Aizawa). A total of 576 measurements were made. There were one to seven determinations per patient with an average of 1.9 measurements per case. In addition to measuring cerebral blood flow (CBF) (ml/100 gm brain/min), cerebral oxygen consumption (CMRO2) (ml/100 gm brain/min), cerebral vascular resistance (CVR) (mm Hg/ml/100 gm brain/min) and cerebral respiratory quotient (CRQ) were also calculated from CBF, mean arterial blood pressure (MABP) and cerebral arteriovenous difference in oxygen (A-VO2). Partial pressures of arterial and venous oxygen and carbon dioxide (PaO2, PvO2, PaCO2, PvCO2) were determined with an IL blood gas analyzer.

CEREBRAL HEMODYNAMICS BEFORE AND AFTER APOPLEXY

In ten patients cerebral hemodynamics were measured both before the apoplectic event and within one month following the event (table 3). For the entire group the average CBF prior to the stroke was 48.5 ± 9.2 and after the stroke was 39.6 ±8.1 (table 3, B). This difference is statistically significant (P <0.05). Changes in CVR (2.37 ± 0.75 to 2.96 ± 0.88), CMRO2 (3.02 ± 0.53 to 2.76 ± 0.67), PV02 and MABP were not significant (table 3).

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HYPERTENSION AND CEREBROVASCULAR DISEASE

In eight patients, measurements were obtained before and after cerebral infarction (fig. 1). CBF decreased in five patients and was unchanged in three. Three patients developed profound hemiplegia associated with clouding of consciousness and exhibited the most marked decline in CBF. In those patients with mild hemiparesis and no alteration in consciousness the CBF decreased to less than 10% of the premorbid value.

**Intracranial Hemorrhage**

Four patients with intracranial hemorrhage (two subarachnoid and two intracerebral) had hemodynamic measurements prior to and within two weeks following the vascular catastrophe (fig. 2). All four patients experienced rapid clouding of consciousness at the onset. In all four the CBF and CMRO₂ decreased markedly after the hemorrhage. Three of the four exhibited a subsequent rise in the CBF with a secondary decline after two years.

**ALTERATIONS IN CEREBRAL HEMODYNAMICS FOLLOWING APoplexy**

Fifty-seven patients had their first hemodynamic measurements within a month following their stroke, and their second measurements at least 30 days after the first determination (fig. 3).

In 45 patients with cerebral infarction the CBF averaged 41.8 ± 6.2 within a month of the stroke. Cerebral blood flow increased in 18 patients, decreased in six patients and remained unchanged in 21 patients 58.3 ± 22.1 days after the stroke. The overall change after the stroke in CBF was a significant increase to 44.5 ± 6.6 (p < 0.01). Neither CVR (2.79 ± 0.58) nor CMRO₂ (2.92 ± 0.54 to 2.96 ± 0.57) were significantly changed. These were further subdivided according to prognosis.

Sixteen patients had experienced mild strokes and were able to resume normal daily activities within two weeks after the onset of cerebral infarction. In this group, the CBF obtained within a month of the onset averaged 47.2 ± 4.3 and was little changed on a subsequent determination (48.5 ± 7.3) 148 days after the stroke.

Thirteen patients had experienced clinically severe episodes of cerebral infarction with marked and transient neurological deficits and exhibited both clouding of consciousness at the

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**Table 2**

| Cerebral Hemodynamics in Hypertension (Accident Group versus Non-Accident Group) |
|---------------------------------|---------------|----------------|----------------|----------------|
| No. of months measured | CBF | MAP | CVR | CVR | CBF | MAP | CVR | CVR |
| 1. Cases without Cerebral or Cardiac Accidents | 139 | 53.0 | 49.6 | 242 | 19.0 | 19.0 | 0.7 | 0.6 |
| 2. Cases with Cerebral or Cardiac Accidents | 119 | 48.4 | 25.2 | 153 | 17.4 | 0.3 | | |

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**Cerebral Infarction**

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YAMAOKA, TAKAGI, OKADA, SAITO

TABLE 3
Pre- and Post-Stroke Changes of Cerebral Hemodynamics (Measurements Taken within 1 Month After Onset)

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Month*</th>
<th>Day†</th>
<th>CBF</th>
<th>MAP</th>
<th>CVR</th>
<th>CMRO₂</th>
<th>PECO₂</th>
<th>PrO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1) Cerebral Infarction (6 cases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.T.</td>
<td>62</td>
<td>13</td>
<td>before</td>
<td>50.7</td>
<td>85</td>
<td>1.68</td>
<td>3.33</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>H.O.</td>
<td>63</td>
<td>49</td>
<td>30</td>
<td>after</td>
<td>35.5</td>
<td>81</td>
<td>2.28</td>
<td>2.45</td>
<td>1.08</td>
</tr>
<tr>
<td>T.T.</td>
<td>69</td>
<td>14</td>
<td>30</td>
<td>before</td>
<td>38.8</td>
<td>116</td>
<td>2.98</td>
<td>2.44</td>
<td>0.92</td>
</tr>
<tr>
<td>S.I.</td>
<td>45</td>
<td>14</td>
<td>3</td>
<td>after</td>
<td>34.3</td>
<td>129</td>
<td>3.76</td>
<td>1.59</td>
<td>0.94</td>
</tr>
<tr>
<td>S.W.</td>
<td>71</td>
<td>38</td>
<td>30</td>
<td>before</td>
<td>50.7</td>
<td>92</td>
<td>1.81</td>
<td>3.42</td>
<td>0.95</td>
</tr>
<tr>
<td>S.N.</td>
<td>59</td>
<td>13</td>
<td>14</td>
<td>before</td>
<td>49.6</td>
<td>120</td>
<td>2.42</td>
<td>2.79</td>
<td>0.99</td>
</tr>
</tbody>
</table>

A-2) Intracranial Hemorrhage (4 cases)
| K.S.  | 54  | 66     | before | 65.6 | 98   | 1.49 | 4.12  | 0.95  |
| S.I.  | 57  | 41     | 11    | after | 37.8 | 84   | 1.22  | 3.18  | 0.97 |
| K.S.  | 67  | 15     | 10    | before | 60.0 | 96   | 1.60  | 2.68  | 1.08 |
| U.K.  | 48  | 3      | 9     | after | 50.6 | 128  | 2.53  | 2.94  | 1.01 |

B) Pre- and Post-Stroke Cerebral Hemodynamics (av. for 10 Cases)

<table>
<thead>
<tr>
<th>Age</th>
<th>Month*</th>
<th>Day†</th>
<th>CBF</th>
<th>MAP</th>
<th>CVR</th>
<th>CMRO₂</th>
<th>PECO₂</th>
<th>PrO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>26.8</td>
<td>48.5</td>
<td>110</td>
<td>2.37</td>
<td>3.02</td>
<td>0.97</td>
<td>36.1</td>
<td>33.4</td>
</tr>
<tr>
<td>After</td>
<td>8.2</td>
<td>17.7</td>
<td>39.6</td>
<td>114</td>
<td>2.96</td>
<td>2.76</td>
<td>2.76</td>
<td>34.5</td>
</tr>
</tbody>
</table>

onset and inability to walk a month later. The initial average CBF determination in this group was 37.5 ± 6.3; 117 days after the infarction there was no substantial increase (39.3 ± 4.1).

Sixteen patients were classified as having had clinically moderate strokes with courses intermediate between the two above-mentioned groups. The initial average CBF within a month of the cerebral infarction was 39.8 ± 3.2; 69.4 days after the stroke the CBF increased significantly to 44.6 ± 4.2.

Twelve patients had intracranial hemorraghes (one subarachnoid and 11 intracerebral). The CBF averaged 43.0 ± 7.1 11.3 days after the hemorrhage. Eighty days after the hemorrhage the average CBF had increased to 51.0 ± 6.4 (nine increases, one decrease and two unchanged), a statistically significant increase.

Following intracranial hemorrhage CVR exhibited a significant decrease (2.71 ± 0.41 to 2.39 ± 0.41) but CMRO₂ showed no significant change (3.29 ± 0.65 to 3.54 ± 0.44).

CORRELATION OF CEREBRAL BLOOD FLOW TO CLINICAL COURSE FOLLOWING CEREBRAL APoplexy

One hundred forty-six patients had CBF determinations in the clinical stage at least one month after the stroke (fig. 4). Of 113 patients with occlusive cerebrovascular disease, 68 have lived a normal life without recurrence during periods of observation of more than one year (average observation time 34.3 months). The CBF in this group averaged 47.1 ± 6.3. Twenty-two patients experienced recurrent
stroke during the period of observation, and the average CBF in this group over one month after the first stroke was 41.0 ± 6.2, a difference of statistical significance (p < 0.01). Five patients remained severely impaired and bedridden seven months after the first stroke and their average CBF was markedly reduced (29.4 ± 5.4). Of the 22 patients who experienced recurrent stroke, 13 had recurrences within one year and had an average CBF of 38.7 ± 0 (fig. 5). This is a significantly lower value than the remaining nine patients who had recurrences more than one year after stroke (44.2 ± 5.5). The average CBF of 33 patients with intracranial hemorrhage were 47.1 ± 6.8, almost equivalent to the value in patients with occlusive cerebrovascular disease without recurrence. No recurrence was observed in this group of cases except for one case of subarachnoid hemorrhage.

Discussion
A decrease in total cerebral blood flow, determined by the N₂O method, has been well documented in patients with cerebrovascular disease.¹⁻⁴

There have been few reports evaluating cerebral hemodynamics in the same patient both before and after a stroke. Therefore, it has not been resolved whether the cerebral circulatory and metabolic derangements were present prior to the stroke or were the result of it.

For the past decade the authors have been measuring cerebral hemodynamics in hypertensive patients without cerebrovascular disease and in patients with cerebrovascular disease. Hemodynamic data have been accumulated in 12 patients both before and after the onset of stroke. In ten of these patients repeat hemodynamic studies were obtained within one month of the stroke and in each a statistically significant decrease in the CBF was noted when compared to the premorbid value. This decrease was most marked in those patients who experienced intracranial hemorrhage or clinically severe cerebral infarction. These ten patients also tended to have a decreased

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YAMAOKA, TAKAGI, OKADA, SAITO

![Graph showing CBF changes](Image)

**Figure 2**

*Pre- and post-stroke CBF changes.*

**Figure 3**

*Post-stroke CBF changes.*

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Stroke, Vol. 3, January-February 1972
HYPERTENSION AND CEREBROVASCULAR DISEASE

Measurements made 1 month or more after stroke

<table>
<thead>
<tr>
<th>Condition</th>
<th>Death bedridden, without improvement</th>
<th>Recurrence of cerebral infarction</th>
<th>Daily life possible w/o recurrence</th>
<th>CMRO₂ observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Occlusive Cerebrovascular Disease</td>
<td>5</td>
<td>22</td>
<td>68</td>
<td>113</td>
</tr>
<tr>
<td>Died bedridden, without improvement</td>
<td>5</td>
<td>22</td>
<td>68</td>
<td>113</td>
</tr>
<tr>
<td>Death due to cancer and other causes</td>
<td>5</td>
<td>22</td>
<td>68</td>
<td>113</td>
</tr>
<tr>
<td>Death due to cancer and other causes (non cerebral circulatory disorders)</td>
<td>5</td>
<td>22</td>
<td>68</td>
<td>113</td>
</tr>
<tr>
<td>(B) Intracranial Hemorrhage</td>
<td>4</td>
<td>22</td>
<td>68</td>
<td>113</td>
</tr>
</tbody>
</table>

FIGURE 4

Correlation of prognosis in stroke with cerebral blood flow.

CMRO₂ after the stroke, but the changes in oxygen consumption were not statistically significant.

That the decrease in CBF in patients with a stroke is due to the stroke itself and did not precede it is suggested by the insignificant difference in CBF between those hypertensive patients who did not progress to clinical cerebrovascular disease and the premorbid values in those who did. The decrease in CBF in the latter group clearly resulted from the stroke.

The decrease in average CBF following a stroke is to be expected from both the impaired blood flow in the infarcted site due to a unilateral hemispheric disturbance and also from the diminished blood flow to the contralateral hemisphere.

Rasmussen and Skinhøj ⁶ injected ⁹⁹Kr into the internal carotid arteries of patients with cerebrovascular disease and noted a decrease in blood flow to the contralateral uninvolved hemisphere. They proposed a mechanism of transneural depression of metabolism of the contralateral hemisphere. Meyer et al. ⁷ ⁸ injected hydrogen-saturated saline into the internal carotid arteries of patients with cerebrovascular disease. They found a decrease in blood flow to both the diseased area and the contralateral hemisphere immediately following infarction. While no recovery of blood flow occurred at the site of infarction, there was a prompt return of blood flow to the contralateral side. It was felt that the most likely mechanism was the neurogenic mechanism or theory of "diaschisis" proposed by Von Monakow ⁰ and Kempinsky, ¹⁰ ¹¹ i.e., the contralateral decrease in blood flow is due to metabolic depression originating in the diseased hemisphere.

Brain edema is another factor possibly involved in the decrease in total cerebral blood flow following stroke. Since CBF decreases most markedly following cerebral hemorrhage, subarachnoid hemorrhage and large infarction (conditions associated with generalized cerebral edema), it may be reasonable to assume that the edema plays a role in the decrease in blood flow.

Lassen, ¹² Paulson, ¹³ and Fieschi ¹⁴ measured local cerebral hemodynamics with ¹³³Xe and found that ischemia or hyperemic foci
develop at the site of the lesion or its margin following cerebral infarction; a decrease in blood flow to the contralateral hemisphere was also noted. The hyperemic foci ("luxury perfusion") occur a short time after the infarction and represent a regional change in hemodynamics and would not be expected to alter significantly measurements of total cerebral blood flow.

In the present study it was found that CBF was the only factor which decreased significantly following a stroke, and it usually demonstrated a statistically significant recovery. Alterations in MABP, CVR, CRQ and CMRO2 were not statistically valid. The authors were unable to demonstrate a change in cerebral metabolism prior to a change in cerebral blood flow. In patients with clinically small cerebral infarctions apparently only a small area is involved in the circulatory disturbance. The CBF is not significantly different from the premorbid value and dementia does not accompany the event. In patients with moderately severe cerebral infarction or with intracranial hemorrhage the CBF decreases markedly at the onset and is associated with a generalized metabolic depression. CBF demonstrates significant recovery within a month. In patients with clinically severe cerebral infarction there is a marked decrease in cerebral blood flow; this group exhibits the poorest recovery of subsequent CBF and demonstrates the persistence of a neurological deficit, personality disturbance and dementia.

Changes in CBF following stroke vary from case to case. Subsequent improvement in CBF could be due to a decrease in cerebral edema or may be due to a reversible functional decrease in the CBF present at the onset. Where there is no improvement in CBF following stroke it is possible that cerebral vessels or metabolism of large aggregate of neurones may have been irreversibly damaged by ischemia at the onset.

It was previously held that in ischemic cerebral tissue the functional properties of the parenchymal cells were the first to be affected,
ignoring any possible deterioration of the vessels themselves with secondary damage to the parenchyma. Ames,16 Chiang,16 and Cantu17 demonstrated that ischemia of 5 to 15 minutes results in marked constriction and obstruction of cerebral vessels; ischemia of the perivascular glial cells led to failure of the sodium transport mechanism with swelling of the glia and irreversible obstruction of the vasculature by these cells ("no-reflow" phenomenon).

Our results suggest that similar mechanisms were operative in our patients when the onset of ischemia and decreased CBF was marked in the whole brain.

Extended observation of our patients indicated that there is a greater likelihood of recurrence of stroke when there is poor recovery of CBF following the initial stroke. It seems likely that the cerebral vessels sustained severe organic damage at the onset of the initial stroke, possibly due to ischemic and swollen perivascular glial cells.

Based on this study, the authors have devised a schema of the alterations of CBF which occur prior to, at the onset of, and following cerebrovascular disease (fig. 6).

In patients with hypertension CBF changes little during years of observation. Immediately following a stroke it decreases abruptly. In patients with cerebral hemorrhage the decrease is marked after the stroke, but its recovery is good during the next two to four months.

In patients with cerebral infarction, the CBF decrease is slight in degree in clinically mild cases with mild deficits; the CBF decrease is great and CBF recovery poor in cases with severe deficits. Cases with moderate deficits follow intermediate courses.

Recurrent cerebral infarction occurred in those cases in which CBF was the most reduced.

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References

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