Hemodilution Improves Cerebral Hemodynamics in Internal Carotid Artery Occlusion

Hiroshi Yamauchi, MD; Hidenao Fukuyama, MD; Masafumi Ogawa, MD; Yasuomi Ouchi, MD; Jun Kimura, MD

Background and Purpose: Hemodilution may be a useful form of therapy for patients with carotid occlusive disease and hemodynamic ischemia. Accordingly, we evaluated the effects of hemodilution on cerebral hemodynamics and oxygen metabolism in patients with carotid artery occlusion.

Methods: Using positron emission tomography, we analyzed regional cerebral blood flow, oxygen extraction fraction, oxygen metabolic rate, and blood volume before and after isovolemic hemodilution in five patients with unilateral internal carotid artery occlusion and minor stroke. Hemodilution was accomplished by phlebotomy of 400 mL and infusion of 400 mL of hydroxyethyl starch.

Results: Before hemodilution, the patients had a significant decrease in blood flow and oxygen transport along with significantly elevated oxygen extraction fraction in the cerebral hemisphere with carotid artery occlusion compared with six control subjects. After hemodilution, the hematocrit and arterial oxygen content decreased from 41.2% and 18.6 mL/dL to 36.3% and 16.5 mL/dL, respectively. Both cerebral blood flow and oxygen transport were increased and oxygen extraction fraction was decreased without any change in oxygen consumption. The degree of increase in blood flow and oxygen transport was positively correlated with the ratio of oxygen extraction fraction to blood volume before hemodilution.

Conclusions: These findings indicate that hemodilution improves oxygen transport as well as blood flow in patients with internal carotid occlusion and decreased perfusion and that this improvement may be more prominent in patients with a severely compromised hemodynamic state. Thus, hemodilution may be useful in patients with hemodynamic ischemia. (Stroke. 1993;24:1885-1890.)

Key Words • carotid artery diseases • hemodilution • hemodynamics • tomography, emission-computed

A fter internal carotid artery (ICA) occlusion, both thromboembolic and hemodynamic mechanisms may have a role in the development of cerebral ischemia. Although antiplatelet therapy may be of value in preventing thromboembolic stroke, it is unlikely to prevent hemodynamic ischemia. Measurement of cerebral blood flow (CBF) by single-photon emission computed tomography (SPECT) with vasodilatory stimuli has the possibility of detecting patients with ICA occlusion who are hemodynamically compromised.1 However, it is unclear how to medically manage such patients with a high risk of hemodynamic ischemia.2

Hemodilution increases CBF in both normal and ischemic brain3,4 and thus has the potential to improve the hemodynamically compromised state of patients with ICA occlusion. However, the effect of hemodilution on cerebral oxygen transport and metabolism remains unclear. In the normal brain, the increase of CBF by hemodilution probably is a physiological regulatory mechanism that maintains oxygen transport to the tissues at a constant level, along with vasodilatation in response to a reduced oxygen content.5,6 Therefore, hemodilution may decrease oxygen transport if the perfusion pressure is low enough, and this would cause maximal vasodilatation.7 In the ischemic brain, however, a direct hemorrhheologic effect is also suggested to augment CBF8 and increase oxygen transport. Therefore, hemodilution may improve oxygen transport in patients with ICA occlusion and low perfusion.

The purpose of this study was to evaluate the effects of isovolemic hemodilution on cerebral hemodynamics and oxygen metabolism in patients with chronic symptomatic ICA occlusion by using positron emission tomography (PET) and to examine the effect of hemodilution on patients in a hemodynamically compromised state.

Subjects and Methods

We studied four men and one woman aged 48 to 68 years (mean±SD, 60.4±7.6 years) who had angiographically proven unilateral ICA occlusion. They consisted of one patient with transient ischemic attacks and four with minor completed strokes. Only subcortical abnormalities were detected in the middle cerebral artery...
TABLE 1. Clinical and Radiographic Data for the Five Patients With Internal Carotid Artery Occlusion

<table>
<thead>
<tr>
<th>Patient/ Age, y/ Sex</th>
<th>Hematocrit (Before/After), %</th>
<th>Complications</th>
<th>Presentation</th>
<th>Neurologic Findings</th>
<th>Angiography (Collateral)</th>
<th>Infarct Size on Computed Tomography, mm&lt;sub&gt;x&lt;/sub&gt;mm</th>
<th>Time Since Latest Ischemic Event, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/59/M</td>
<td>44.9/40.3</td>
<td>DM</td>
<td>Amaurosis fugax (left, twice)</td>
<td>Normal</td>
<td>Left ICA occlusion (leptomeningeal)</td>
<td>Left frontal subcortex (7x10)</td>
<td>5</td>
</tr>
<tr>
<td>2/63/M</td>
<td>43.4/36.4</td>
<td>HT</td>
<td>Stroke with slight disability</td>
<td>Left upper limb drift, dysarthria</td>
<td>Right ICA occlusion (A com.)</td>
<td>Right corona radiata (6x20)</td>
<td>5</td>
</tr>
<tr>
<td>3/64/M</td>
<td>41.5/37.7</td>
<td>DM</td>
<td>Stroke with mild disability</td>
<td>Mild transcortical motor aphasia</td>
<td>Left ICA occlusion (P com., leptomeningeal)</td>
<td>Left frontal subcortex (13x32)</td>
<td>1</td>
</tr>
<tr>
<td>4/68/F</td>
<td>37.6/33.6</td>
<td>HT</td>
<td>TIA (once), stroke with mild disability</td>
<td>Mild right hemiparesis, mild transcortical motor aphasia</td>
<td>Left ICA occlusion (leptomeningeal)</td>
<td>Left frontal subcortex (10x30)</td>
<td>6</td>
</tr>
<tr>
<td>5/48/M</td>
<td>38.6/33.7</td>
<td>HT</td>
<td>TIA (once), stroke with moderate disability</td>
<td>Moderate right hemiparesis, moderate transcortical sensory aphasia</td>
<td>Left ICA occlusion (A com.)</td>
<td>Left P1 hypoplasia</td>
<td>4</td>
</tr>
</tbody>
</table>

M indicates male; F, female; DM, diabetes mellitus; HT, hypertension; TIA, transient ischemic attack; ICA, internal carotid artery; A com., anterior communicating artery; P com., posterior communicating artery; A1, A1 segment of the anterior cerebral artery; and P1, P1 segment of the posterior cerebral artery.

(MCA) territory on computed tomography. The clinical and neuroradiological data are summarized in Table 1.

The specifications of our PET scanner have been reported elsewhere. In brief, the device has four rings containing 192 bismuth germinate detectors and provides seven tomographic slices at one time. Its best spatial resolution is 7.6 mm (full-width half-maximum) at the center of the scanning field, and the axial resolution is 12 mm at the center. The scanning procedure was as follows. Before the study, a germanium 68–gallium 68 transmission scan was performed over 20 minutes for attenuation correction. CBF was then determined while the subject continuously inhaled oxygen 15-labeled carbon dioxide (370 to 555 MBq/min) through a mask. Measurement of the cerebral metabolic rate of oxygen (CMRO₂) and the oxygen extraction fraction (OEF) was done during the continuous inhalation of oxygen 15-labeled oxygen at 740 to 1110 MBq/min. Data were collected for 5 minutes. A single breath of oxygen 15-labeled carbon monoxide (2.96 GBq) was used to measure cerebral blood volume (CBV). We calculated CBF, CMRO₂, and OEF based on the steady-state method. Functional images were reconstructed as 64x64 pixels, with each pixel representing 2.5x2.5 mm. The subjects underwent phlebectomy of 400 mL and infusion of 400 mL of 6% hydroxyethyl starch over 30 to 40 minutes for isovolemic hemodilution. PET studies were repeated immediately after hemodilution. In all patients, PET was performed at least 1 month after the latest ischemic event.

We analyzed three tomographic planes, which were 4.0, 6.6, and 8.2 cm above and parallel to the orbitomeatal line and corresponded to the basal ganglia and thalamus, the body of the lateral ventricles, and the centrum semiovale, respectively. For determination of the cerebral regions of interest (ROIs), each of the three images was used to place a total of 18 to 20 circular ROIs, each 11 pixels (0.6875 cm²), over the cortex. According to the atlas of Kretschmann and Weinrich, the ROIs in all three images were in the distribution of the anterior cerebral artery (ACA), the MCA, and the posterior cerebral artery (PCA), as well as in the watershed areas between the ACA and MCA (anterior watershed [AWS]) and the MCA and PCA (posterior watershed [PWS]). The hemispheric value was calculated as the average of the MCA, AWS, and PWS values weighted by region size.

In each ROI, the product of CBF and the total oxygen content of arterial blood (CaO₂) was computed as an index of oxygen transport to the cerebral tissue, and the ratio of CBF to CBV was determined as an index of cerebral perfusion pressure. The CaO₂ was calculated as (1.39×Hb×SaO₂) + (0.0031×Pao₂), where Hb is the hemoglobin concentration, SaO₂ is the arterial oxygen saturation, and Pao₂ is the arterial oxygen tension. The response to changes in hematocrit with hemodilution was defined as the absolute change in CBF or CBF×CaO₂ with respect to the absolute change in hematocrit from before to after hemodilution.

Results obtained in the patients before and after hemodilution were compared with those obtained in six age-matched normal volunteers (four men and two women; mean±SD age, 52±18 years) using the Mann-Whitney U test after the Kruskal-Wallis one-way analysis of variance. We defined a statistically significant value of P<.0125 (0.05/4) using Bonferroni's correction for multiple comparisons. We also compared the values obtained before and after hemodilution using the paired Wilcoxon signed-rank test. Differences of P<.05 were considered
significant. The relations between the CBF and CBF×CaO2 response and the PET parameters before hemodilution were analyzed using Pearson’s correlation coefficient and partial correlation coefficient.

### Results

The physiological parameters obtained in the patients before and after hemodilution and in the control subjects are listed in Table 2, including the arterial hematocrit, arterial hemoglobin concentration, PaCO2, PaO2, SaO2, CaO2, pH, and mean arterial blood pressure. The values obtained in the patients before and after hemodilution were not significantly different from the control values (Kruskal-Wallis one-way analysis of variance). Hemodilution significantly reduced the mean hematocrit from 41.2% to 36.3%, the hemoglobin concentration from 13.8 to 12.2 g/dL, and the CaO2 from 18.6 to 16.5 mL/dL. However, the blood gases, pH, and mean arterial blood pressure showed no significant differences after hemodilution.

Table 3 shows the mean hemispheric values of CBF, CMRO2, OEF, CBV, CBF/CBV ratio, and CBF×CaO2 before and after hemodilution. Before hemodilution, the patients showed significant decreases in CBF, the CBF/CBV ratio, and CBF×CaO2 as well as a significant elevation in OEF in the hemisphere with ICA occlusion compared with the control subjects. The CBF and CBF/CBV ratio were significantly decreased in the hemisphere contralateral to ICA occlusion as well. After hemodilution, only CBF, the CBF/CBV ratio, and CBF×CaO2 in the hemisphere with ICA occlusion were significantly different from the control values.

Fig 1 shows the mean hemispheric values of CBF, CBF×CaO2, CMRO2, and OEF before and after hemodilution in each patient. Hemodilution significantly increased CBF and CBF×CaO2 and significantly de-

### Table 2. Physiological Data Obtained in Patients and in Control Subjects Before and After Hemodilution

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>41.2±3.1</td>
<td>36.3±2.8*</td>
<td>38.3±5.0</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.8±1.2</td>
<td>12.2±1.1*</td>
<td>13.0±1.8</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>38.7±2.2</td>
<td>39.9±3.3</td>
<td>40.9±2.8</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>90.3±6.6</td>
<td>93.9±9.4</td>
<td>102.6±24.4</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>97.2±0.6</td>
<td>97.3±1.1</td>
<td>97.0±1.2</td>
</tr>
<tr>
<td>CaO2, mL/dL</td>
<td>18.6±1.6</td>
<td>16.5±1.5*</td>
<td>17.8±2.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.43±0.02</td>
<td>7.43±0.02</td>
<td>7.40±0.05</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>109.9±11.2</td>
<td>110.3±6.8</td>
<td>100.6±8.8</td>
</tr>
</tbody>
</table>

MABP indicates mean arterial blood pressure. Values are mean±SD.

*P<.05, different from the value before hemodilution by the paired Wilcoxon signed-rank test.

### Table 3. Values of Regional CBF, CMRO2, OEF, CBV, and CBF/CBV Ratio in Affected and Unaffected Cerebral Hemispheres of Patients and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemisphere</th>
<th>Before</th>
<th>After</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, mL·100 g⁻¹·min⁻¹</td>
<td>Occluded</td>
<td>26.5±2.5*</td>
<td>33.4±2.3†</td>
<td>41.4±4.7</td>
</tr>
<tr>
<td></td>
<td>Patent</td>
<td>32.8±2.6†</td>
<td>42.1±2.0</td>
<td></td>
</tr>
<tr>
<td>CMRO2, mL·100 g⁻¹·min⁻¹</td>
<td>Occluded</td>
<td>2.55±0.39</td>
<td>2.62±0.36</td>
<td>3.14±0.58</td>
</tr>
<tr>
<td></td>
<td>Patent</td>
<td>2.93±0.37</td>
<td>2.81±0.28</td>
<td></td>
</tr>
<tr>
<td>OEF, %</td>
<td>Occluded</td>
<td>51.8±3.4†</td>
<td>46.9±2.7</td>
<td>42.2±5.1</td>
</tr>
<tr>
<td></td>
<td>Patent</td>
<td>48.9±4.9</td>
<td>41.9±2.2</td>
<td></td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>Occluded</td>
<td>3.91±0.37</td>
<td>3.62±0.45</td>
<td>3.24±0.38</td>
</tr>
<tr>
<td></td>
<td>Patent</td>
<td>3.49±0.47</td>
<td>3.14±0.45</td>
<td></td>
</tr>
<tr>
<td>CBF/CBV, min⁻¹</td>
<td>Occluded</td>
<td>6.9±0.4*</td>
<td>9.4±1.0†</td>
<td>13.1±2.1</td>
</tr>
<tr>
<td></td>
<td>Patent</td>
<td>9.9±1.3†</td>
<td>14.1±2.1</td>
<td></td>
</tr>
<tr>
<td>CBF×CaO2, mL·100 g⁻¹·min⁻¹</td>
<td>Occluded</td>
<td>4.94±0.79†</td>
<td>5.53±0.64‡</td>
<td>7.36±1.11</td>
</tr>
<tr>
<td></td>
<td>Patent</td>
<td>6.11±0.33</td>
<td>6.95±0.52</td>
<td></td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; CMRO2, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CBV, cerebral blood volume; and CaO2, total oxygen content of arterial blood. Values are mean±SD.

*P<.002, †P<.005, ‡P<.0125, different from controls by Mann-Whitney U test.
creased OEF in the bilateral hemispheres. CMRO$_2$ showed no significant changes.

The CBF$\times$Cao$_2$ response to a change in hematocrit was significantly correlated with the CBF response ($r=.974$, $P<.0001$). Fig 2 shows the relation between the CBF$\times$Cao$_2$ response and the OEF/CBV ratio before hemodilution. The CBF$\times$Cao$_2$ response was correlated positively with the value of the OEF/CBV ratio. Hemispheres with a high OEF or a low CBV value had a tendency to show more marked improvement. The hemispheres with a high OEF value showed the most improvement. However, a substantial CBF$\times$Cao$_2$ response was also found in some hemispheres with a relatively low OEF value. These hemispheres also showed a decrease in CBV with a relative high OEF/CBV ratio. The partial correlation coefficient indicated that there was a significant relation of the CBF$\times$Cao$_2$ response to OEF (Rho=.734, $P=.024$) and CBV (Rho$=.764$, $P=.016$), with CBV and OEF as the respective partial variables.

**Discussion**

We showed that ICA occlusion with a low CBF and a submaximal increase in OEF achieved an increase in both CBF and oxygen transport in the affected hemisphere with hemodilution. Subsequently, the elevated OEF decreased without a change in CMRO$_2$, indicating that hemodilution improved the oxygen supply, which had been inadequate for tissue demands. Thus, hemodilution may have a beneficial hemodynamic effect in stroke patients with ICA occlusion showing hemodynamic compromise, although it does not change oxygen transport in the normal human brain.$^5,14$

Hemodilution improved the hemodynamic state of all the patients. However, the responses of CBF and CBF$\times$Cao$_2$ to a change in hematocrit were variable and correlated positively with the value of the OEF/CBV ratio before hemodilution, indicating that the effect of hemodilution was determined by the hemodynamic state before hemodilution in each patient. The OEF/CBV ratio shows a biphasic change in the course of perfusion pressure reduction due to ICA occlusion.$^1$ In the early stage, where autoregulatory vasodilatation maintains CBF, an increase in CBV without a change in OEF causes a decrease in the OEF/CBV ratio. The minimum value is reached at the limit of autoregulation when the vessels show nearly maximal dilatation.$^{13}$ Further reductions in the perfusion pressure then produce a decrease in CBF with a compensatory increase in OEF. CBV increases further to its maximal level and thereafter may passively decrease as vessels begin to collapse. These changes lead to an increase in the
are complex and mutually related under ischemic conditions, the OEF/CBV ratio may indicate the total capacity of hemodilution to increase CBF.

Although a high hematocrit is considered to be a risk factor for cerebral infarction,10 the hematocrit values in patients with ICA occlusion on antiplatelet therapy did not relate to the risk of stroke.20 This finding may have resulted from not taking account of the cerebral hemodynamics. In one study, watershed infarcts accounted for 72% of delayed strokes in patients with ICA occlusion,21 and most of the infarcts were suggested to result from hemodynamic mechanisms that included elevated hematocrit as an important factor. The difference in the cerebral hemodynamics determined at high and low hematocrit values in this study suggests that an elevation of hematocrit will worsen the hemodynamic state in patients with ICA occlusion. An increase in hematocrit may be an important risk factor for cerebral ischemia in patients who are hemodynamically compromised. In the clinical setting, the hemodynamic state of patients can be evaluated by paired CBF measurements with SPECT before and after the application of a vasodilatory stimulus.1

Risk factors, including a high hematocrit, should be managed with reference to the underlying hemodynamic state of each patient. Antiplatelet therapy is unlikely to prevent hemodynamic stroke. We must seek other specific medical therapies for patients with carotid occlusive disease who exhibit hemodynamic compromise in the form of low perfusion with increased OEF. Modifying the hematocrit may be a useful management strategy for patients with ICA occlusion showing hemodynamic ischemia.

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