Hemodynamics in Internal Carotid Artery Occlusion Examined by Positron Emission Tomography

Hiroshi Yamauchi, MD, Hidenao Fukuyama, MD, Jun Kimura, MD, Junji Konishi, MD, and Masakuni Kameyama, MD

Using positron emission tomography in nine patients with minor strokes, unilateral internal carotid artery occlusion, and good collateral circulation through the anterior portion of the circle of Willis, we analyzed regional cerebral blood flow, cerebral metabolic rate of oxygen, oxygen extraction fraction, and cerebral blood volume. These studies allowed quantification of the regional hemodynamic status, especially in relation to watershed areas. Compared with eight normal controls, the patients had significantly \((p<0.01)\) decreased regional cerebral blood flow in the middle cerebral artery territory and the surrounding watershed areas of the occluded hemisphere. The oxygen extraction fraction rose with the distance from the anterior portion of the circle of Willis, attaining the highest value in the superior parietal and posterior temporo-occipital watershed area. A concomitant decrease in the cerebral blood flow/cerebral blood volume ratio suggested reduction in the mean blood flow velocity, whereby elevated blood viscosity would be more liable to reduce cerebral blood flow. These findings suggest hemodynamic vulnerability of the watershed areas after internal carotid artery occlusion in persons with good collateral circulation through the anterior portion of the circle of Willis. Our results also emphasize the importance of systemic hemodynamic factors such as blood pressure and circulating blood volume in the genesis of watershed infarction. \((\text{Stroke} 1990;21:1400-1406)\)

Positron emission tomography (PET) allows quantification of the regional hemodynamic and metabolic status of the brain in patients with ischemic brain diseases; specifically, PET can measure the oxygen extraction fraction (OEF), providing vital information on the balance between oxygen supply and demand, which in turn serves as an index of the oxygen carriage reserve.\(^1\)

Although autopsy results\(^2\) and x-ray computed tomographic (CT) studies\(^3,4\) have characterized the watershed infarcts that develop after internal carotid artery (ICA) occlusion, the pathogenesis and pathophysiology of watershed infarction remains controversial.\(^5\) In ICA occlusion, this type of infarction affects distant regions most severely. This finding has lead to the assumption that hemodynamic factors play a major role. However, no study has yet documented the relation between the occurrence of watershed infarction and the hemodynamic state in persons with ICA occlusion.

The purpose of our study was to evaluate the regional hemodynamic status of patients after ICA occlusion, especially in relation to the watershed areas, and to elucidate whether these areas are in fact hemodynamically vulnerable.

**Subjects and Methods**

We studied nine patients (eight men and one woman) aged 46–74 (mean±SD 57.9±7.6) years who had unilateral ICA occlusion and angiographically proven collateral circulation through the anterior portion of the circle of Willis. The patients comprised one person with no symptoms, three with transient ischemic attacks, and five with minor completed strokes. All except the asymptomatic patient had patchy areas of high intensity in the centrum semiovale, corresponding to the subcortical watershed area in the occluded hemisphere, on \(T_2\)-weighted magnetic resonance images. These abnormalities were mostly undetectable on x-ray CT scans, which showed only minor subcortical abnormalities <1.5 cm in diameter in the middle cerebral artery (MCA).
Clinical and Radiographic Data for Nine Patients With Unilateral Internal Carotid Artery Occlusion

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Associated conditions</th>
<th>Presentation</th>
<th>Physical examination</th>
<th>Angiography (four-axis)</th>
<th>Computed tomography</th>
<th>Magnetic resonance imaging (high-intensity area on T2-weighted image)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/58/M</td>
<td>Hypertension</td>
<td>Amaurosis fugax (L, twice), TIAs (frequent)</td>
<td>Slight R hemiparesis</td>
<td>L ICA occlusion, mild R ICA stenosis</td>
<td>No infarct</td>
<td>L subcortical MCA watershed area</td>
</tr>
<tr>
<td>2/46/M</td>
<td>Diabetes mellitus</td>
<td>Minor stroke</td>
<td>Mild L hemiparesis</td>
<td>R ICA occlusion, mild L ICA stenosis</td>
<td>R corona radiata infarct</td>
<td>R subcortical MCA watershed area</td>
</tr>
<tr>
<td>3/57/M</td>
<td>None</td>
<td>TIA (twice)</td>
<td>Slight R hemiparesis</td>
<td>L ICA occlusion, mild R ICA stenosis</td>
<td>No infarct</td>
<td>L subcortical MCA watershed area</td>
</tr>
<tr>
<td>4/52/M</td>
<td>Hypertension</td>
<td>Minor stroke</td>
<td>Mild L hemiparesis</td>
<td>R ICA occlusion</td>
<td>R centrum semiovale infarct</td>
<td>R subcortical MCA watershed area</td>
</tr>
<tr>
<td>5/58/F</td>
<td>None</td>
<td>TIA (once), minor stroke</td>
<td>Mild R sensory disturbance</td>
<td>L ICA occlusion</td>
<td>L centrum semiovale infarct</td>
<td>L subcortical MCA watershed area</td>
</tr>
<tr>
<td>6/57/M</td>
<td>None</td>
<td>TIA (once)</td>
<td>Normal</td>
<td>R ICA occlusion</td>
<td>No infarct</td>
<td>R subcortical MCA watershed area</td>
</tr>
<tr>
<td>7/74/M</td>
<td>Hypertension</td>
<td>Minor stroke</td>
<td>Mild L hemiparesis</td>
<td>L ICA occlusion</td>
<td>L centrum semiovale infarct</td>
<td>L subcortical MCA watershed area</td>
</tr>
<tr>
<td>8/56/M</td>
<td>Angina pectoris</td>
<td>Minor stroke</td>
<td>Mild L hemiparesis</td>
<td>R ICA occlusion</td>
<td>R corona radiata infarct</td>
<td>R subcortical MCA watershed area</td>
</tr>
<tr>
<td>9/63/M</td>
<td>None</td>
<td>No symptoms</td>
<td>Normal</td>
<td>R ICA occlusion</td>
<td>No infarct</td>
<td>No high-intensity area</td>
</tr>
</tbody>
</table>

All TIAs and strokes were related to occluded hemisphere.

Pt, patient number; M, male; F, female; L, left; R, right; TIA, transient ischemic attack; ICA, internal carotid artery; MCA, middle cerebral artery.

territory. Clinical and neuroradiological data for the patients are summarized in Table 1.

Details of our PET scanner have been reported elsewhere. In brief, the device has four rings, each containing 192 BiGe detectors, providing seven tomographic slices at one scanning process. The device offers the best spatial resolution of 7.6 mm in full-width half-maximum at the center of the scan field and an axial resolution of 12 mm at the center. Blood was sampled through a cannula in the antecubital artery three times during each scanning process for determining oxygen-15 activity and arterial blood gases. Prior to the study, a germanium-68-gadolinium-68 transmission scan was performed for 20 minutes for attenuation correction. In every study, we determined calibration factors between the PET scanner and the well counter as well as the calibration factor for cross-planes of the PET scanner. The data were processed with a Hitachi image processing computer (Tokyo) using system subroutines to reconstruct 64x64 pixel functional images, each pixel representing 2.5x2.5 mm.

Cerebral blood flow (CBF) was determined while the subject continuously inhaled 10–15 mCi C15O/min through a mask. Measurements of the cerebral metabolic rate of oxygen (CMRO2) and OEF required continuous inhalation of 20–30 mCi O15O/min. Data were collected for 5 minutes. A single breath of 80 mCi C15O was used to measure the cerebral blood volume (CBV). We calculated CBF, CMRO2, and OEF based on the steady-state method, and we corrected CMRO2 and OEF by the value of CBV.

In all patients, PET was performed at least 1 month after the latest ischemic event. Results in each vascular region from the patient group were compared with those from eight normal controls (mean±SD ages 39±14 years). The physiologic state of the patients and controls during PET, including Paco2, PaO2, hematocrit, arterial hemoglobin concentration, and mean arterial blood pressure, are given in Table 2.

As shown in Figure 1, we analyzed images in three tomographic planes, 5.0, 6.6, and 8.2 cm above and parallel to the orbitomeatal line (i.e., the levels of the basal ganglia and thalamus, the body of the lateral ventricle, and the centrum semiovale). Each image

Baseline Physiologic Data for Nine Patients With Unilateral Internal Carotid Artery Occlusion and Eight Normal Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pco2 (mm Hg)</td>
<td>40.3±6.2</td>
<td>41.1±2.4</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>90.2±8.9</td>
<td>96.7±6.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38.5±4.0</td>
<td>41.0±4.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.0±1.4</td>
<td>14.0±1.4</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>96.2±10.4</td>
<td>89.3±6.4</td>
</tr>
</tbody>
</table>

Values are mean±SD.
FIGURE 1. Diagrams of tomographic planes containing 18–20 circular regions of interest placed over cerebral cortex divided into five areas: territories of anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) and watershed areas between ACA and MCA (anterior watershed, AWS) and between MCA and PCA (posterior watershed, PWS). These five areas are separated by lines in each diagram.

was examined by placing 18–20 circular regions of interest, each containing 11 pixels (0.785 cm²), over the gray matter of the cortex. According to the atlas of Kretschmann and Weinrich, the regions of interest in all three images included the territories of the anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) and the watershed areas between the ACA and MCA (the anterior watershed) and between the MCA and PCA (the posterior watershed).

Statistical analyses included analysis of variance using Bonferroni's correction, with differences giving p<0.05 regarded as significant.

Results
Table 3 shows the mean±SD values for regional CBF, CMRO₂, OEF, CBV, and the CBF/CBV ratio for the patients and controls. In the hemisphere ipsilateral to the ICA occlusion, the patients had a significantly (p<0.01) decreased regional CBF in the anterior watershed, MCA territory, and particularly the posterior watershed. These three areas also demonstrated a significantly increased OEF and a significantly decreased CBF/CBV ratio, with the maximal changes detected in the posterior watershed.

Figure 2 shows OEF in each tomographic plane. In the hemisphere ipsilateral to the ICA occlusion, OEF was greatest in the posterior watershed regardless of tomographic plane. In addition, OEF changed with the distance from the anterior portion of the circle of Willis, being greater in the upper than in the lower plane in each region.

Figure 3 shows the CBF/CBV ratio in each tomographic plane. In the hemisphere ipsilateral to the ICA occlusion, the CBF/CBV ratio was lowest in the posterior watershed for all tomographic planes.

As shown in Figures 2 and 3, no OEF or CBF/CBV ratio gradient, especially no upward gradient, was observed in the controls, while their posterior watershed had a tendency for a higher OEF than the anterior watershed or MCA territory.

In three patients with mild ICA stenosis contralateral to the ICA occlusion, average OEF in the posterior watershed was markedly elevated (to 0.59, 0.60, and 0.62, with the maximum values of 0.61, 0.61, and 0.66). Each maximum value was found in the posterior watershed of the uppermost plane. As in the six patients without contralateral ICA stenosis, OEF increased toward the upper plane in an area remote from the circle of Willis, but this tendency was accentuated in the three patients with stenosis. The average CBF/CBV ratio was depressed (to 6.0, 5.3, and 5.2) in the posterior watershed in the hemisphere ipsilateral to the ICA occlusion, showing a reciprocal relation to OEF.

Discussion
One problem in our study was the inadequate matching for age between our patients and controls. With age, CBF, CMRO₂, and CBV decline, while OEF and the CBF/CBV ratio do not change. Therefore, the effect of aging on these parameters is important in comparing the pathophysiologic states of the aged with those in younger controls. Our results focus primarily on the localized alterations in hemodynamics in persons with ICA occlusion, especially in relation to the watershed areas. Therefore, we did not carefully consider the influence of aging.

Various types of watershed infarcts have been reported after ICA occlusion. Autopsy or CT studies elucidated a few common areas of involvement (i.e., the superior frontal, superior parietal, and lateral occipital regions). Morphologic studies, however, have failed to reveal the time course of hemodynamic changes or the physiologic mechanisms underlying vascular insufficiency.

In one study, watershed infarction accounted for 72% of delayed strokes in patients with ICA occlusions. Hemodynamic mechanisms considered important in this series included elevated hematocrit, severe heart disease with episodes of decreased cardiac output and syncope, and severe disease of the contralateral ICA. In animal experiments, ICA occlusion resulted in the loss of cerebral autoregulation, leading to ischemic changes in the parietal watershed area caused by hypotension.
Although PET studies of ICA occlusion abound, few have focused on the regional hemodynamic status in watershed areas. Samson et al reported a relatively higher OEF in the posterior watershed area ipsilateral to an ICA occlusion. Baron et al reported a case of “misery perfusion syndrome” with collateral circulation through the ophthalmic artery following ICA occlusion; this abnormal elevation of OEF was most marked in the parieto-occipital watershed area. The authors mentioned that CBF and CMRO₂ were significantly decreased without an elevation in OEF in 12 patients, one with an MCA occlusion and 11 with ICA occlusions. In their series, the infarcts that developed in most patients prevented accurate evaluation of the watershed areas because infarcted tissue could not be included in the regions of interest. Therefore, their data might have shown only unremarkable elevations of OEF in the posterior watershed area. Similarly, only a small percentage of patients have shown an elevated OEF in the averaged MCA or hemispheric value in most previous works. Regional analysis of the watershed areas, if performed in such studies only for noninfarcted patients, would have revealed elevated OEF in many cases.

Serving as an index of the oxygen carriage reserve, OEF gives information on the balance between the oxygen supply to the brain and the demand from the nervous tissue. Areas with an increased OEF exhibit poor autoregulatory or CO₂ responsiveness. At the site of dysautoregulation, CBF promptly decreases with a reduction in cerebral perfusion pressure. An elevated OEF implies vulnerability to a reduction in cerebral perfusion pressure and a tendency to develop cerebral infarction owing to hemodynamic factors. Our data suggest that areas far from the anterior portion of the circle of Willis have higher OEFs and therefore the greatest vulnerability to ischemic insults. This is particularly true in the parieto-occipital and posterior temporo-occipital watershed areas.

The CBF/CBV ratio is proposed as an index of the perfusion reserve of the cerebral circulation and is the reciprocal of the mean transit time. According to this definition, the blood flow velocity would decrease with a reduction in the CBF/CBV ratio. If blood viscosity were elevated in such areas, the combined effect of increased viscosity and slowed velocity would lead to a marked reduction in CBF.
with a risk of developing ischemic accidents. In our study, the parieto-occipital and posterior temporoparietal watershed areas had reduced CBF/CBV ratios; therefore, an elevated hematocrit or a reduced cardiac output would promptly compromise blood flow in these areas. Areas with a decreased CBF/CBV ratio have a higher risk of developing infarcts as a consequence of additional factors disturbing the circulatory environment.

The deleterious influence of bilateral ICA disease on cerebral hemodynamics has been pointed out by several authors. In our series, three patients had mild stenosis of the ICA contralateral to the occluded ICA. The watershed areas of these patients exhibited prominent alterations in OEF and the CBF/CBV ratio. As mentioned above, marked changes on these two indexes suggest threatening ischemic insults. The coexistence of contralateral ICA lesions further compromises the perfusion state.
Hemodynamics in internal carotid artery occlusion examined by positron emission tomography.
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