Altered Cerebral Hemodynamics and Metabolism in Takayasu’s Arteritis with Neurological Deficits

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Background and Purpose: Takayasu’s arteritis is a nonspecific arteritis involving major cerebral arteries. The aim of our study is to examine cerebral hemodynamics and metabolism in Takayasu’s arteritis with neurologic symptoms.

Methods: We measured cerebral blood flow and metabolism using positron emission tomography in seven patients (14 to 59 years of age) with Takayasu’s arteritis who developed transient ischemic attacks (2 patients), ischemic stroke (4) or putaminal hemorrhage with multiple brain infarction (1).

Results: All patients had severe stenosis or occlusion of one or more major cerebral arteries. There were no significant differences in the values of cerebral blood flow, oxygen extraction fraction, and cerebral blood volume in the infarcted and noninfarcted hemisphere. By contrast, the value of cerebral metabolic rate for oxygen in the infarcted hemisphere was markedly reduced (1.87 mL/100 mL per minute, P<.01) compared with controls. Mean transit time in the infarcted hemisphere was significantly greater than in the noninfarcted one, both in patients and controls (P<.01 and P<.05, respectively).

Conclusions: Collateral blood flow to the hemisphere without brain damage may be relatively well developed in Takayasu’s arteritis, although hemodynamic reserve as well as oxygen metabolism were impaired in the infarcted hemisphere with ischemic lesions. (Stroke. 1993;24:1501-1506.)

Key Words • arteritis • hemodynamics • tomography, emission computed

Takayasu’s arteritis is a nonspecific, inflammatory arteritis involving the aorta and its major branches and is more prevalent in young Asian females. Clinical manifestations vary depending on the sites and severity of the occlusive vascular lesions.1-7 Stroke may be an important and predictive complication for the prognosis in such patients.2,3,8 However, changes in cerebral hemodynamics and metabolism in relation to neurological disorders in these patients are still not fully understood. Progression of stenosis or occlusion of the major cerebral arteries may be gradual, and cerebral blood flow in Takayasu’s arteritis is thought to be well preserved on the basis of clinical and angiographic findings.1-4 Patients with neurological deficits may demonstrate more impaired intracranial circulation and brain metabolism than those without. We performed neuroradiological examination and brain hemodynamic and metabolic study using positron emission tomography (PET) in patients with Takayasu’s arteritis who developed neurological symptoms.

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Subjects and Methods

Seven patients with Takayasu’s arteritis having neurological symptoms (one man and six women aged 14 to 59 years; mean±SD, 36.1±16.1) were admitted to the Second Department of Internal Medicine of Kyushu University Hospital for the evaluation of their cerebral hemodynamics and metabolism. The diagnosis of Takayasu’s arteritis was obtained by the characteristic findings on angiography and serological study.2-4 Clinical profiles of these patients are summarized in Table 1. Two (patients 2 and 3) were bilaterally “pulseless,” and three (patients 1, 4, and 5) were pulseless or had weakness of pulsation on one radial artery. Carotid bruit was noted in six (patients 1, 2, 3, 5, 6, and 7), but none of them had aortic valvular disease. Systemic complications were associated in three patients: moderate anemia in patients 5 and 7, arterial hypertension in patients 6 and 7, and renal insufficiency in patient 7. Six healthy men with normal brain computed tomographic (CT) appearance (aged 26 to 36 years; mean±SD, 29.7±4.3) were used as controls.

The six cases of ischemic episodes consisted of four patients with minor stroke (patients 1, 2, 3, and 6), one with transient ischemic attack (patient 4), and one with dizzy spells (patient 5). Brain CT scan and cerebral angiography including the aorta and its major branches were performed in all patients, and three were also studied by brain magnetic resonance imaging. Three patients (patients 1, 2, and 3) showed deep-seated small to medium brain infarcts in the left hemisphere, and in
two patients multiple subcortical infarcts in both hemispheres were demonstrated on CT scan. Patient 7 developed brain hemorrhage in the left putamen, and the remaining two had normal CT findings.

Cerebral blood flow (CBF) and metabolism were studied using the HEADTOME-III device (Shimadzu Corp, Kyoto, Japan), which had a transaxial resolution of 8.2 mm and an axial resolution of 13 mm full width at half maximum. CBF, oxygen extraction fraction (OEF), and cerebral metabolic rate for oxygen (CMRO₂) were measured using the ¹⁵O steady-state method, with continuous infusion of H₂¹⁵O or inhalation of C¹⁵O₂ and H₂¹⁵O. Cerebral blood volume (CBV) was measured using a single inhalation of H₂¹⁵O or C¹⁵O₂. Oxygen extraction fraction and CMRO₂ were corrected by CBV. Mean transit time was calculated as CBV/CBF. A transmission scan with a ⁶⁸Ge/⁶⁷Ga ring source was obtained from each patient for attenuation correction. For the ¹⁵O steady-state method, five cross-sectional planes 20, 35, 50, 65, and 80 mm above the orbitomeatal line were scanned simultaneously for 6 minutes. CBF, OEF, CMRO₂, and CBV were obtained bilaterally, as previously reported. These parameters were measured similarly in controls.

The values are presented as mean ± SD. Mean values of each variable on PET, arterial blood gases, and hemoglobin content in the seven patients were compared with those in the controls using two-tailed unpaired t test or ANOVA and subsequent Scheffé's method. Differences giving a value of P < .05 were significant.

### Results

Age and arterial blood gases were not significantly different between patients and controls. Hemoglobin content was significantly smaller in patients (P < .05) (Table 2).

Angiographic findings are schematically represented in the Figure. Extracranial arteries were more severely affected on the left side than on the right, compatible with previous reports. Six patients had occlusions in the major branches of the aorta. The nine hemispheres vascularized by occluded or severely stenotic arteries were observed (the right hemisphere in patients 2, 3, 5, and 6; the left hemisphere in patients 1, 2, 3, 4, and 6), and the remaining five hemispheres were vascularized by normal or low-grade stenotic arteries. Two patients (4 and 5) showed subclavian steal phenomenon. In
Aortic arch and its major branches, circle of Willis and its branches in seven patients with Takayasu’s arteritis. Filled segments indicate occluded vessels, or could not be assessed on angiography. Subclavian steal phenomena are observed in cases 4 and 5. OA, ophthalmic artery; 1, internal carotid artery; 2, external carotid artery; 3, anterior cerebral artery; 4, middle cerebral artery; 5, posterior cerebral artery; 6, basilar artery; 7, vertebral artery; 8, common carotid artery; 9, innominate artery; 10, subclavian artery.

patient 6, the right anterior cerebral artery and the left internal carotid artery were completely occluded.

Table 3 shows individual hemispheric PET parameters in the seven patients with Takayasu’s arteritis. There were no significant differences between the hemispheres with occluded or severely stenotic arteries and those without (data not shown). Results of cerebral blood flow and metabolism are summarized in Table 4. Although the sites of occlusion or stenosis on cerebral angiography and the brain lesions demonstrated on CT scan in the patients were heterogeneous, there were no significant differences between the right and left hemispheric values of each variable in the patients (Table 4) as well as in the controls (data not shown). Thus, we compared averaged left-right hemispheric values of each variable between patients and control subjects (Table 4). Results based on the averaged left-right hemispheric values were the same as those in the separate analyses on each hemisphere. The left-right averaged hemispheric CBF was 33.6 mL/100 mL per minute (92.8% of control), which was not significantly different from that in the controls. The averaged hemispheric values for OEF, CBV, and mean transit time in patients also did not differ from those in controls. In contrast, the value of CMRO₂ of the averaged hemisphere was reduced by more than 20% of the control: 2.02 mL/(100 mL/min) (77.7% of control).

Of the seven patients, three had infarcts on the left side, two had bilateral infarcts, and two had normal CT findings. Thus, brain infarctions were observed totally in seven hemispheres (infarcted hemisphere), and in the remaining seven hemispheres no brain lesions were revealed on CT scan (noninfarcted hemisphere). The data obtained in the infarcted and noninfarcted hemispheres in patients and the averaged left-right hemispheric values in control subjects are shown in Table 5. CMRO₂ of the infarcted hemisphere in patients was significantly smaller than the averaged hemispheric value in controls ($P<.01$). Mean transit time of the infarcted hemisphere in patients was significantly prolonged as compared with that of the noninfarcted side in patients and controls ($P<.01$ and $P<.05$, respectively). There was no significant difference in the values of CBF, OEF, and CBV among the three groups (Table 5).

**Discussion**

In Takayasu’s arteritis with occlusion or stenosis of major extracranial cerebral arteries, CBF is supplied through collaterals such as the thyrocervical trunk, anterior spinal arteries, and several unnamed vessels, in addition to patent cervical arteries.2–4 The circle of Willis may also play an important role.6 However, it

<table>
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<tr>
<th>Patient</th>
<th>CBF, mL/100 mL per min</th>
<th>CMRO₂, mL/100 mL per min</th>
<th>OEF, %</th>
<th>CBV, mL/100 mL</th>
<th>MTT, s</th>
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<td>R</td>
<td>L</td>
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<tr>
<td>1</td>
<td>41.6</td>
<td>37.6</td>
<td>2.42</td>
<td>2.19</td>
<td>37.1</td>
</tr>
<tr>
<td>2</td>
<td>38.9</td>
<td>36.9</td>
<td>2.67</td>
<td>2.49</td>
<td>35.1</td>
</tr>
<tr>
<td>3</td>
<td>22.0</td>
<td>21.8</td>
<td>1.71</td>
<td>1.79</td>
<td>48.9</td>
</tr>
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<td>34.1</td>
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</tr>
<tr>
<td>5</td>
<td>39.4</td>
<td>38.8</td>
<td>1.86</td>
<td>1.83</td>
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</tr>
<tr>
<td>6</td>
<td>30.1</td>
<td>34.5</td>
<td>1.56</td>
<td>1.49</td>
<td>26.8</td>
</tr>
<tr>
<td>7</td>
<td>31.8</td>
<td>31.4</td>
<td>1.85</td>
<td>1.70</td>
<td>50.9</td>
</tr>
</tbody>
</table>

**PET** indicates positron emission tomography; **CBF**, cerebral blood flow; **CMRO₂**, cerebral metabolic rate for oxygen; **OEF**, oxygen extraction fraction; **CBV**, cerebral blood volume; and **MTT**, mean transit time.
remains unclear whether collateral circulation is able to maintain intracranial hemodynamics and brain metabolism. Although all patients in the present study had occlusion or severe stenosis of the major extracranial cerebral arteries, more severely affected on the left side, ischemic brain lesions were heterogeneous (none to multiple). There were no significant differences in all of the PET parameters in the following comparisons: between the hemisphere vascularized by occluded or severely stenotic arteries and those without, and between the left and right hemispheres. Thus, in Takayasu’s arteritis, the development of brain ischemia might not directly relate to the ipsilateral cervical arterial lesions but rather importantly depend on the degrees of characteristic development of extracranial and intracranial collateral pathways. Therefore, in such circumstances, it is important to measure CBF and cerebral perfusion pressure to know collateral circulation rather than angiographic evidence.

Because parameters in the hemispheres without brain lesion on CT did not significantly differ from those in the controls, the cerebral vasculature was not engaged in any adaptive mechanism of a defect in blood supply. This suggests a relatively well-preserved cerebral hemodynamic situation via the appropriately developed collateral pathways in the noninfarcted hemisphere of patients with Takayasu’s arteritis. The normal value of CBF may be partly due to the lower blood viscosity in our patients. Insignificantly reduced value of CMRO2 in the noninfarcted side may be partly due to the remote effect of the contralateral brain lesions.19 In Takayasu’s arteritis, cerebrovascular disease has not been reported to be a frequent complication, despite multiple occlusions of major cervical arteries.2,3 Thus, it is also possible that collateral circulation is able to maintain cerebral hemodynamics and metabolism in patients with Takayasu’s arteritis without cerebrovascular complication.

On the other hand, CMRO2 was significantly decreased in the infarcted hemisphere. The infarcted lesions in our cases involved basal ganglia or subcortical areas, which have been reported to decrease brain metabolism in the homologous cortical area or in the whole hemisphere.10-22 Chronic suppression of oxygen metabolism or some neuronal loss due to cerebral ischemia, even with normal CT findings, is also postulated as a cause of brain hypometabolism.23,24 Although the reduction of CBF in the infarcted side was not significant, the value may be relatively overestimated because of the low hemoglobin content.23,25,26 Thus, the low CMRO2 (1.87 mL/100 mL per minute) can be directly related to the infarcted areas.

In the infarcted hemisphere of our patients, OEF and CBV were not altered whereas the mean transit time was significantly prolonged compared with that in the noninfarcted side as well as that in the controls, which suggests the existence of impaired hemodynamic reserve. Recent studies on cerebral circulation using PET in other carotid occlusive diseases have also reported the presence of impaired cerebral hemodynamics.15,24,27-30 Under these circumstances, reduction in

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**Table 4. Hemispheric Values of Positron Emission Tomographic Study in Patients With Takayasu’s Arteritis and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Takayasu’s Arteritis (n=7)</th>
<th>Controls (n=6)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Right Hemisphere</td>
<td>Left Hemisphere</td>
</tr>
<tr>
<td>Cerebral blood flow, mL/100 mL per min</td>
<td>34.0±6.8</td>
<td>33.2±5.8</td>
</tr>
<tr>
<td>Cerebral metabolic rate for oxygen, mL/100 mL per min</td>
<td>2.08±0.44*</td>
<td>1.96±0.36*</td>
</tr>
<tr>
<td>Oxygen extraction fraction, %</td>
<td>38.9±8.4</td>
<td>37.8±9.6</td>
</tr>
<tr>
<td>Cerebral blood volume, mL/100 mL</td>
<td>4.42±1.13</td>
<td>4.66±1.21</td>
</tr>
<tr>
<td>Mean transit time, s</td>
<td>7.97±2.31</td>
<td>8.52±1.96</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<.01, †P<.05, respectively, different from controls.

†P<.01 different from noninfarcted side, by ANOVA and subsequent Scheffe’s method.

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**Table 5. Comparison of Each Variable Between Infarcted and Noninfarcted Hemisphere in Takayasu’s Arteritis**

<table>
<thead>
<tr>
<th></th>
<th>Takayasu’s Arteritis</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Infarcted Side (n=7)</td>
<td>Noninfarcted Side (n=7)</td>
</tr>
<tr>
<td>Cerebral blood flow, mL/100 mL per min</td>
<td>32.0±5.3</td>
<td>35.2±6.8</td>
</tr>
<tr>
<td>Cerebral metabolic rate for oxygen, mL/100 mL per min</td>
<td>1.87±0.36*</td>
<td>2.18±0.38</td>
</tr>
<tr>
<td>Oxygen extraction fraction, %</td>
<td>38.5±11.9</td>
<td>38.2±4.8</td>
</tr>
<tr>
<td>Cerebral blood volume, mL/100 mL</td>
<td>5.12±1.24</td>
<td>3.96±0.68</td>
</tr>
<tr>
<td>Mean transit time, s</td>
<td>9.66±2.00††</td>
<td>6.83±0.83</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<.01, †P<.05, ††P<.01, respectively, different from controls.

†P<.01 different from noninfarcted side, by ANOVA and subsequent Scheffe’s method.
CBF is offset by an increased flow in the remaining arteries and maximal vasodilatation of intracerebral resistance vessels. This phenomenon is known as autoregulation and is partly controlled by increased CVR or prolonged mean transit time. Mean transit time is reported to be a more sensitive parameter of reduced cerebral perfusion pressure than CVR and remains relatively constant over a widely changed CBF, even in a status of low hemoglobin content. In the infarcted hemisphere in Takayasu’s arteritis, prolonged mean transit time without increased OEF or CVR suggests that cerebral circulation is just above the autoregulatory lower limit with maximal vasodilatation. The lack of misery perfusion state in our patients can reflect relatively well-developed collaterals, which contrasts with the severe cervical arterial lesions as previously reported.15,24,27-30 since such gradually developed abundant collateral pathways are one of the specific features in Takayasu’s arteritis.1-4

It is uncertain, however, whether impaired hemodynamic reserve chronically aggravates brain metabolism in patients with (multiple) cervical arterial occlusion, although impaired cerebral circulation has been reported in some patients with chronic vascular ischemia or dementia.3 However, the pathophysiology of such stroke is likely to be complex: hemodynamic, as in our patients, but also local thrombosis or artery-to-artery embolism, as reported in major stroke. Recurrence of stroke is uncommon, probably due to the gradual development of abundant collaterals. However, cerebral hemodynamics may be chronically insufficient in Takayasu’s arteritis, as shown in the cases of hypersensitive carotid sinus reflex or hypotensive carotid sinus reflex or hypotensive carotid sinus reflex or hypotensive arteritis,8 and reduced hemodynamic reserve chronically aggravates brain metabolism in patients with Takayasu’s arteritis, which may be related to insufficient collaterals.3 However, the pathophysiology of such stroke is likely to be complex: hemodynamic, as in our patients, but also local thrombosis or artery-to-artery embolism, as reported in major stroke. Recurrence of stroke is uncommon, probably due to the gradual development of abundant collaterals. However, cerebral hemodynamics may be chronically insufficient in Takayasu’s arteritis, as shown in the cases of hypersensitive carotid sinus reflex or hypotensive ophthalmamoangiopathy.1-3 Thus, any small reduction in blood pressure may cause development of cerebral ischemia even in the chronic stage of this illness.

In advanced Takayasu’s arteritis, hypertension, anemia, and renal insufficiency are commonly associated important complications. Arterial blood pressure is one of the determinants of the prognosis of Takayasu’s arteritis, and reduced hemodynamic reserve with hypertension may predispose individuals to cerebral ischemia and stroke. These factors may also contribute to impaired cerebral circulation as well as brain hypometabolism in Takayasu’s arteritis.

In Takayasu’s arteritis, surgical treatments are widely applied to improve the hemodynamic situation, but this is mainly based on angiographic evidence. This attitude should now be reevaluated by measuring CBF and cerebral metabolism.

Acknowledgments

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References


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