Surgically Induced Angiogenesis to Compensate for Hemodynamic Cerebral Ischemia

Tadashi Nariai, MD; Ryuta Suzuki, MD; Yoshiharu Matsushima, MD; Koichi Ichimura, MD; Kimiyoshi Hirakawa, MD; Kenji Ishii, MD; Michio Senda, MD

Background and Purpose  The ischemic brain may stimulate angiogenesis to compensate for impaired circulation. We examined the conditions promoting such angiogenesis to provide the basis for surgical treatment.

Methods  The degree of cerebral hemodynamic stress was studied in patients with moyamoya disease using the stable xenon-enhanced computed tomographic acetazolamide tolerance test and positron emission tomography. Patients were subjected to surgery in which scalp arteries were placed on the cerebral cortex without vessel-to-vessel anastomosis. Formation of the newly vascularized collateral network connecting the implanted artery to cortical arteries was assessed angiographically 12 to 17 months after surgery.

Results  Preoperative average resting cerebral blood flow for cortex that developed revascularization was not significantly different from that for cortex that did not. However, cortex that developed revascularization had an average preoperative increase of blood flow by acetazolamide treatment of \(-3.29\pm4.6\) mL/min per 100 cm\(^3\) \((n=20)\), which was significantly less \((P=.0034)\) than that of cortex that did not show revascularization \((20.7\pm4.3\) mL/min per 100 cm\(^3\); \(n=9)\). Good revascularization developed when the cortex showed increase of blood flow by acetazolamide treatment of less than 0 (steal phenomenon). Preoperative positron emission tomography data indicated that revascularization developed when the cortex was under "misery perfusion." Postoperative hemodynamics were ameliorated by revascularization.

Conclusions  Angiogenesis to connect the implanted scalp arteries to the cerebral cortical arteries was selectively initiated when ischemia of hemodynamic origin existed. (Stroke. 1994;25:1014-1021.)

Key Words  • cerebral blood flow • cerebral vascularization • moyamoya disease • tomography, emission-computed • xenon

Ischemic tissue in need of more oxygen delivery can compensate for impaired circulation by angiogenesis,\(^{1,2}\) which leads to an increase in the vascular bed.\(^{3,4}\) Such an increase has been observed in chronic cerebral ischemia in both animals\(^5\) and clinical subjects.\(^6\)

We have treated more than 120 patients with chronic cerebral ischemia, primarily those with moyamoya disease, using encephalo-duro-arterio-synangiosis (EDAS), a procedure developed by one of the authors (Y.M.).\(^7,8\) In this procedure a scalp artery is placed on the surface of the brain without direct vessel-to-vessel anastomosis (schematically shown in Fig 1). Angiogenesis is induced at the site of the implanted vessel, which connects the external carotid system to cerebral cortical arteries (indirect bypass surgery). In this procedure the cortical arteries become perfused from the external carotid system, with favorable clinical outcome in many cases.\(^8,14\) However, there are cases in which the cortical artery is not perfused or is poorly perfused by the implanted vessel.\(^11,14\) To determine the cerebral hemodynamic condition in which angiogenesis at the site of the implanted vessel is initiated, we examined the degree of cerebral hemodynamic stress before surgery with the stable xenon-enhanced computed tomographic (Xe/CT) acetazolamide challenge test\(^15,18\) and positron emission tomography (PET). The degree of revascularization of cortical arteries and alterations in hemodynamics were evaluated postoperatively. Part of this data has been presented previously in abstract form.\(^19\)

Subjects and Methods

Sixteen patients with moyamoya disease and one patient with unilateral intracranial internal carotid occlusion with a moyamoya-appearing vessel ranging in age from 2 to 54 years were subjected to Xe/CT cerebral blood flow (CBF) study and/or PET before surgery. The characteristics of the patients are described in Table 1. Thirteen patients presented symptoms of transient ischemic attack or convulsion without apparent neurological deficit. Four of those patients had lesions of cerebral infarction examined with x-ray CT or magnetic resonance imaging. Four other patients had neurological deficit caused by cerebral infarction. However, the onset of symptoms was not clear for the latter four patients, and their symptoms and CT findings were stable during the 2-month (approximate) preoperative period. Therefore, the preoperative examination and the operation were performed during the chronic stage of the disease.

The Xe/CT CBF study was performed using the 4-minute wash-in, 3-minute wash-out method with 30% stable xenon gas.\(^20,22\) For the preparation of cold xenon gas, commercially distributed pure xenon gas (Xenopure, Teisan Co Ltd) was mixed with room air to obtain a 30% concentration using an automatic xenon gas inhalator (Xetron-V, Anzai So-Gyo Co Ltd). Regional CBF in the resting state \([\text{rCBF}(R)]\) and 15 minutes after intravenous injection of acetazolamide (20 mg/kg) (Diamox, Lederle) \([\text{rCBF}(AT)]\) (both expressed in milliliters per minute per 100 cubic centimeters) was measured for
all patients. Regional increase in CBF after acetazolamide treatment was expressed as \( \Delta A T \), as follows:

\[ \Delta A T = r\text{CBF(AT)} - r\text{CBF(R)} \]

The PET study was performed with a Headtome-IV scanner (Shimadzu Corp), which provides 14 slices of tomographic images with an interval of 0.5 mm. Arterial catheters were inserted into the radial artery for blood sampling. The transmission data were acquired with a rotating germanium-68 rod source for attenuation correction. Regional CBF, cerebral oxygen metabolism \( (r\text{CMRO}_2) \), and oxygen extraction fraction \( (r\text{OEF}) \) were measured using continuous inhalation of \( ^{15}\text{O}_2 \)

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Symptom</th>
<th>Cerebral Infarction</th>
<th>Follow-up Method</th>
<th>Branches With Revascularization/Branches Implanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>M</td>
<td>TIA (frequent)</td>
<td>+ (bilateral)</td>
<td>Xe</td>
<td>1/2</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>F</td>
<td>TIA in the past</td>
<td>-</td>
<td>Xe</td>
<td>0/2</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>F</td>
<td>TIA (infrequent)</td>
<td>-</td>
<td>Xe</td>
<td>2/3</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>M</td>
<td>TIA (infrequent)</td>
<td>-</td>
<td>Xe</td>
<td>2/2</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>M</td>
<td>TIA (frequent)</td>
<td>+ (bilateral)</td>
<td>Xe</td>
<td>1/2</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>F</td>
<td>TIA (infrequent)</td>
<td>-</td>
<td>PET</td>
<td>2/2</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>M</td>
<td>TIA (frequent)</td>
<td>+ (unilateral)</td>
<td>Xe</td>
<td>2/2</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>F</td>
<td>TIA (infrequent)</td>
<td>-</td>
<td>PET</td>
<td>1/1 (unilateral IC lesion)</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>F</td>
<td>TIA (infrequent)</td>
<td>+ (unilateral)</td>
<td>Xe</td>
<td>3/3</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>F</td>
<td>TIA (frequent)</td>
<td>-</td>
<td>Xe and PET</td>
<td>3/3</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>F</td>
<td>Hemiparesis, visual field defect</td>
<td>+ (unilateral)</td>
<td>Xe</td>
<td>2/2</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>F</td>
<td>TIA (infrequent)</td>
<td>-</td>
<td>Xe and PET</td>
<td>0/2</td>
</tr>
<tr>
<td>13</td>
<td>24</td>
<td>M</td>
<td>Hemiparesis</td>
<td>+ (unilateral)</td>
<td>Xe</td>
<td>1/2</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>F</td>
<td>Hemiparesis</td>
<td>+ (unilateral)</td>
<td>Xe</td>
<td>2/2</td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>F</td>
<td>TIA in the past</td>
<td>-</td>
<td>PET</td>
<td>2/2</td>
</tr>
<tr>
<td>16</td>
<td>43</td>
<td>M</td>
<td>Convulsion</td>
<td>-</td>
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<td>0/2</td>
</tr>
<tr>
<td>17</td>
<td>54</td>
<td>F</td>
<td>Hemianopsia</td>
<td>+ (unilateral)</td>
<td>Xe and PET</td>
<td>1/2</td>
</tr>
</tbody>
</table>

\( \text{TIA} \) indicates transient ischemic attack (all patients followed up in this study had bilateral or unilateral transient muscle weakness); \( \text{Xe} \), stable xenon-enhanced computed tomographic acetazolamide challenge test; PET, positron emission tomography; and IC, internal carotid.
and $^{18}$O$_2$ with the table look-up technique. Arterial blood and plasma radioactivity were measured with continuous sampling of arterial blood. Regional cerebral blood volume (rCBV) was measured by a 3-minute inhalation of $^{15}$O and a PET scan after equilibration. The rOEF and rCMRO$_2$ were corrected for rCBV.$^{27}$ The PET data were analyzed using an image-analysis software system (DR. VIEW) on Stellar GS2000 equipment (Asahi Kasei Co Ltd).

All patients with moyamoya disease received bilateral EDAS regardless of age, symptoms, or CT findings using a parietal branch of the superficial temporal artery (STA) and/or an anterior branch of the STA as a donor.$^{7,8,10}$ Because moyamoya is a bilateral progressive disease,$^{20,29}$ we have nonselectively performed the procedure bilaterally for all patients with moyamoya disease. The operative procedure is schematically described in Fig 1. Briefly, the scalp artery with the strip of galea is freed from the pericranium. Two burr holes made below the proximal and the distal ends of the freed artery are connected to open the skull. The strip of galea, including the scalp artery, is sutured to the incised edge of the dura mater. The artery and the strip of galea are laid on the arachnoid membrane, and the bone flap is replaced and fastened in place (Fig 1, right panel). Note that the flow of scalp artery is maintained after the operation and that the arachnoid membrane is not opened.

Twelve to 17 months after the operation, follow-up angiography was performed. The degree of angiogenesis at the site of the implanted STA was evaluated by measuring the vascularized area (in square centimeters) on the arterial phase of a selective external carotid angiogram with a digital planimeter (Uchida-Yoko Co Ltd) because this area reflects the capacity of a newly formed vascular network. The obtained value was considered approximate because this is smaller than the actual area projected on the brain surface. After revascularization from the implanted STA to the cerebral cortex had been demonstrated angiographically, follow-up Xe/CT and/or PET was performed.

For the analysis of regional data of preoperative and postoperative Xe/CT and PET, slices including the upper margin of the lateral ventricles (usually approximately 7 cm above the orbitomeatal line) were used. The region of interest was outlined as a cortical strip of 1 cm in width extending 1 cm bilaterally from the craniotomy edge (Fig 2). All values are expressed as mean±SEM. Statistical analysis was performed using Student's $t$ test and paired $t$ test. Statistical significance was defined as $P<.05$.

**Results**

**Clinical and Angiographic Outcome of Surgery**

Thirty-six STA branches were implanted in 17 patients (Table 1). Eleven of these branches did not show any revascularization of the cortical arteries on postoperative selective external carotid angiogram. Two branches had stenosis at the proximal end of the craniotomy, and in these two patients clinical symptoms worsened. However, clinical symptoms attributable to areas supplied by the other 9 branches were unchanged. In contrast, when angiographic evidence of revascularization of the cortical arteries was present (25 branches), clinical symptoms (usually transient ischemic attack) attributable to areas supplied by 9 branches disappeared, those supplied by 7 branches improved (decreased frequency of transient ischemic attack), and those supplied by 9 branches were unchanged (Table 2). As we have nonselectively performed the procedure bilaterally for all patients with moyamoya disease based on this principle, 9 branches were implanted to the hemisphere that did not cause apparent clinical symp-

**Table 2. Clinical and Angiographic Outcome of 36 Implanted Branches**

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Angiographic Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disappeared</td>
<td>9</td>
</tr>
<tr>
<td>Improved</td>
<td>7</td>
</tr>
<tr>
<td>No change</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Worsened</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinical outcome is shown for symptoms originating from areas where scalp arteries were implanted. Branches implanted on side of brain that did not cause any clinical symptoms are indicated in parentheses.

Facial constriction of the implanted arteries was observed angiographically at the craniotomy site.
When the approximate area of revascularization measured on the postoperative external carotid angiogram was plotted against preoperative resting CBF and ΔAT (Fig 3), the extent of revascularization was found to be dependent on preoperative ΔAT but not on preoperative resting CBF. Also, it appears that there is a threshold for ΔAT to initiate good revascularization; this value is approximately 0 to 5 mL/min per 100 cm². Therefore, a negative value of ΔAT (steal phenomenon) is an important sign that predicts good postoperative revascularization. Postoperative resting CBF (43.9 ± 3.1 mL/min per 100 cm²; n = 20) and ΔAT (18.8 ± 3.4 mL/min per 100 cm²; n = 20) in cortices that received indirect bypass surgery were both significantly elevated (P = .03 and P = .0003, respectively) postoperatively in patients with angiographic evidence of revascularization.

Preoperative and Postoperative Evaluation With Positron Emission Tomography

Fourteen STA branches were implanted in seven patients. Five of these branches did not show any revascularization of the cortical arteries on postoperative selective external carotid angiogram. Angiographic evidence of revascularization of the cortical arteries was present for 9 branches (Table 1). Preoperative rCBF, rOEF, and rCBV of cortices in which a scalp artery was implanted were plotted against the approximate area of revascularization as measured on postoperative selective external carotid angiogram (Fig 4). Revascularization was shown to develop when the cerebral cortex had elevated OEF and CBV values. It should be noted that resting CBF alone cannot predict the result. In other words, angiogenesis develops when the cerebral cortex is under "misery perfusion." It appears that there is a threshold for OEF and CBV to initiate good revascularization; the threshold for OEF is approximately 0.45, and that for CBV is approximately 5.5%.

Patient 10 in Table 1 is a 15-year-old girl with moyamoya disease who presented with frequent transient weakness of right or left extremities without cerebral infarction. Her preoperative PET study (Fig 5) indicated decreased CBF and increased OEF and CBV, particularly in the bilateral frontoparietal cortex. Two STA branches on the left side and one STA branch on the right side were implanted.
implanted. Preoperative CBF values in the operative fields were 29.2, 29.5, and 32.1 mL/min per 100 cm$^3$ for the right frontal, left frontal, and left parietal regions, respectively. Preoperative OEF values in the operative fields were 0.49, 0.52, and 0.51 for the right frontal, left frontal, and left parietal regions, respectively. Preoperative CBV values in the operative fields were 5.8%, 6.0%, and 6.6% for the right frontal, left frontal, and left parietal regions, respectively. Postoperative external carotid angiography (Fig 6a and 6b) indicated prominent revascularization of the middle cerebral artery through implanted STAs. Postoperative CBF increased, and the OEF (0.46, 0.45, and 0.46 for the right frontal, left frontal, and left parietal regions, respectively) and CBV (5.2%, 3.4%, and 3.4% for the right frontal, left frontal, and left parietal regions, respectively) values decreased, which showed the value to be less than or close to the aforementioned threshold value (Fig 5). Frequency of transient ischemic attack markedly decreased postoperatively.

Patient 17 in Table 1 is a 54-year-old woman who presented with left homonymous hemianopsia of gradual onset and had right occipital infarction. She was diagnosed as having moyamoya disease and was referred to our department. Her preoperative PET study (Fig 7) indicated decreased CBF on both sides (31.5 mL/min per 100 cm$^3$ in the right parietal region and 37.2 mL/min per 100 cm$^3$ in the left parietal region). Laterality of OEF (0.47 on the right and 0.43 on the left) and CBV (6.6% on the right and 4.3% on the left) was observed. Although the parietal branch of STA was implanted bilaterally based on our principle of nonselective bilateral operation, good revascularization was observed only on the right side (Fig 6c), where OEF and CBV exceeded the aforementioned threshold range, and not on the left side (Fig 6d). Postoperative CBF increased, and OEF (0.40) and CBV (5.2%) values in the right parietal region were lower than the aforementioned threshold values. Laterality of OEF and CBV observed on preoperative PET disappeared in the postoperative PET study (Fig 7).

In both cases, preoperative misery perfusion (decreased CBF and increased OEF and CBV) was corrected by indirect bypass surgery.

### Discussion

In this study we obtained the following results. First, angiogenesis was promoted selectively at the site of a scalp artery placed on the surface of the brain when the ischemic cerebral cortex was under chronic hemodynamic stress, which is defined as misery perfusion when demonstrated by PET or defined as decreased vascular reserve when demonstrated by the Xe/CT acetazolamide challenge test. Second, when angiogenesis developed postoperatively, parameters expressing cortical hemodynamics improved and clinical symptoms improved or stabilized. Third, angiogenesis did not develop in the absence of hemodynamic stress regardless of the decreased resting CBF.

These results may be clinical evidence to support previously reported experimental data that showed that live brain tissue under chronic hypoxic conditions initiated angiogenesis promoted by a certain growth factor to maintain oxygen delivery. Also, our results provide the basis for surgical treatment for chronic
cerebral ischemic disease performed without direct vessel-to-vessel anastomosis.\textsuperscript{7,31-33}

From 1980 to the present, we have treated chronic cerebral ischemic disease, mainly moyamoya disease, with EDAS.\textsuperscript{7,8} To date in our institute, 161 sides in 82 children with moyamoya disease, 36 sides in 19 adults with moyamoya disease, 7 children with unilateral internal carotid occlusion, and 2 adults with atherosclerotic internal carotid occlusion have been treated with this procedure. Even without direct vessel-to-vessel anastomosis, a newly formed vascular network connects the STA to the cerebral cortical arteries\textsuperscript{7,9-13,34} and many patients with moyamoya disease and a limited number of patients with chronic cerebral ischemia of atherosclerotic origin\textsuperscript{31,33,35,36} benefit from such surgically induced angiogenesis. However, we have experienced cases in which this procedure did not initiate a newly vascularized network.\textsuperscript{11,14} Our present analysis could provide the quantitative parameter that can predict the surgical result of this procedure.

Through measuring these parameters, we can use indirect bypass surgery more effectively for the treatment of chronic cerebral ischemia. If selection of patients is properly performed using PET\textsuperscript{6-30} or a tolerance test such as CO\textsubscript{2} response\textsuperscript{37-38} or acetazolamide response\textsuperscript{39-41} combined with quantitative CBF measurement methods such as stable Xe/CT or single-photon emission-computed tomography using an appropriate tracer, a successful surgical result will be expected for most cases. However, if surgery is performed based only on resting CBF, there is the possibility that patients who do not need more oxygen delivery because of impaired cerebral function\textsuperscript{42-43} will also be operated on. In this case, no treatment effect is expected. Because chronic hemodynamic ischemia (misery perfusion or decreased vascular reserve) is observed not only in patients with...
moyamoya disease but also in some patients with chronic cerebral ischemia of atherosclerotic origin. Indirect bypass surgery can be a procedure to restore impaired cerebral hemodynamics regardless of the cause of chronic ischemia. Further research to specify the promoter of surgically induced angiogenesis, such as several growth factors that have previously been reported, may also be beneficial in regard to understanding this phenomenon and applying it to the treatment of chronic cerebral ischemic disease.

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