Long-Term Prognosis of Medically Treated Patients With Internal Carotid or Middle Cerebral Artery Occlusion Can Acetazolamide Test Predict It?

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Background and Purpose—The importance of hemodynamic parameters for predicting outcome in patients with occlusive carotid disease remains controversial. The present study was aimed at testing the hypothesis that regional cerebrovascular reactivity (rCVR) to acetazolamide can be a reliable predictor of subsequent ischemic stroke in medically treated patients with internal carotid artery or middle cerebral artery occlusion.

Methods—Seventy-seven symptomatic patients were enrolled in this prospective, longitudinal cohort study. All patients met inclusion criteria of cerebral angiography, no or localized cerebral infarction on MRI or CT, and no or minimal neurological deficit. Regional cerebral blood flow (rCBF) and rCVR to acetazolamide were quantitatively determined by $^{133}$Xe SPECT. All patients were categorized into 4 types on the basis of SPECT studies.

Results—During an average follow-up period of 42.7 months, 16 total and 7 ipsilateral ischemic strokes occurred. The annual risks of total and ipsilateral stroke in patients with decreased rCBF and rCVR were 35.6% and 23.7%, respectively, risks that are higher than those in other types of patients. When strokes were categorized into patients with and without decreased rCBF and rCVR, Kaplan-Meier analysis revealed that the risks of total and ipsilateral stroke in patients with decreased rCBF and rCVR were significantly higher than in those without ($P<0.0001$ and $P=0.0001$, respectively, log-rank test). Relative risk conferred by decreased rCBF and rCVR was 8.0 (95% CI, 1.9 to 34.4) for ipsilateral stroke and 3.6 (95% CI, 1.4 to 9.3) for total stroke.

Conclusions—Decreased rCBF and rCVR to acetazolamide may identify a subgroup of patients who have a higher risk of subsequent ischemic stroke when treated medically. (Stroke. 2001;32:2110-2116.)

Key Words: acetazolamide ■ carotid arteries ■ cerebral blood flow ■ outcome ■ reactivity

There is increasing evidence that cerebral hemodynamics is an important factor in determining the long-term outcome of patients with occlusive carotid artery disease.1–3 Elevated oxygen extraction fraction (OEF) is shown to be a key parameter to detect a subgroup of patients with compromised hemodynamics with PET. Thus, the annual risk of recurrent ischemic stroke in patients with elevated OEF is significantly higher than in those with normal OEF.2,3

On the other hand, cerebrovascular reactivity (CVR) to vasodilators such as acetazolamide and CO$_2$ is also used to evaluate cerebral perfusion reserve with SPECT, xenon CT, or transcranial Doppler sonography.4–14 Although CVR is supposed to be an alternative parameter for predicting long-term outcome, its validity is still controversial.5,6,10,12–14 That is, 4 of 6 previous studies concluded that patients with impaired reactivity to acetazolamide or CO$_2$ had high risk of subsequent ischemic stroke (see Table 3).5,6,12,13 In those studies, patients with impaired reactivity to acetazolamide or CO$_2$ had an annual rate of between 11% and 18% of ipsilateral stroke recurrence, although patients with preserved reactivity had an annual rate of between 0% and 2.2%. However, 2 other studies from the same group reached the opposite conclusion.10,14 Thus, they reported that no strokes were observed during a follow-up period of 1.5 years in 51 patients, 20 of whom had impaired reactivity to acetazolamide.10 Subsequently, Yokota et al14 from the same group also reported that there was no significant difference in cumulative recurrence-free survival rate between 55 patients with and 50 patients without impaired reactivity to acetazolamide, concluding that acetazolamide reactivity was not valuable for predicting patient prognosis.

Some reasons for the different conclusions from these 6 studies have been pointed out, including small sample size, short follow-up periods, withdrawal of a significant number of patients, and methodology of data analysis.5,6,10,12–14 Most previous studies were retrospective. Another problem in discussing the usefulness of...
acetazolamide reactivity is the patient population studied. Of the 6 studies, 3 included patients with significant stenosis of the internal carotid artery (ICA) or middle cerebral artery (MCA). However, it is well known that stenotic lesion may cause ischemic stroke through either a hemodynamic or an embolic mechanism. It is not so easy to distinguish the underlying mechanism in patients with ICA or MCA stenosis, even if they have a critical reduction in cerebral perfusion pressure (CPP). More important, as Yonas et al. indicated, qualitative assessment of acetazolamide reactivity by IMP SPECT, used in 2 of the 6 studies, is known to have low sensitivity and specificity for detecting patients with a compromised reserve. According to their report, quantitative analysis revealed that 11 of 62 patients (18%) who were not considered to be compromised by qualitative criteria had a steal response to acetazolamide and that the positive predictive value of the qualitative method was 50%. Therefore, it is possible that patients were misclassified by qualitative analysis in regard to acetazolamide reactivity.

Hence, in the present study, we aimed to determine whether CVR to acetazolamide could be a reliable predictor of subsequent ischemic stroke in medically treated patients with occlusive carotid diseases. From these observations, we decided to prospectively enroll only patients with occlusion of the ICA or MCA and to quantitatively measure blood flow and CVR to acetazolamide to avoid the above-mentioned problems. For this purpose, regional cerebral blood flow (rCBF) was determined by the $^{133}$Xe inhalation method and SPECT, because the methodology is simple and easy to use to quantify blood flow.

**Subjects and Methods**

**Patients**

This study analyzed 77 patients treated at Hokkaido University Hospital and its affiliated hospitals between April 1990 and December 1999. There were 58 men and 19 women with a mean age of 64.0 years. They suffered ipsilateral ischemic attacks, including transient ischemic attack in 42 patients, reversible ischemic neurological deficits in 10 patients, and minor completed stroke (Rankin Scale score 1 to 2) in 25 patients. Cerebral angiography revealed occlusion of the cervical ICA in 62 patients and of the horizontal portion of the MCA in 15 patients. Plain CT scan or T2-weighted MRI demonstrated no or, if any, minimal infarct in the territory of the occluded arteries. We excluded patients with cardioembolic infarction, aortitis syndrome, and moyamoya disease.

**SPECT Measurements**

rCBF was measured ≥4 weeks after the last ischemic episode in all patients. Using the $^{133}$Xe inhalation method and SPECT (HEADTOME SET-031, Shimadzu Co), we quantitatively measured rCBF before and 15 minutes after injection of 10 mg/kg IV acetazolamide (acetazolamide test). rCBF was calculated by the sequential picture method described by Kanno and Lassen. To evaluate cerebral hemodynamics, 4-cm-diameter circular regions of interest were designated in the territory of the MCA in 15 patients. Plain CT scan or T2-weighted MRI demonstrated no or, if any, minimal infarct in the region of the ipsilateral MCA territories were classified into type 1 in 39 patients, type 2 in 14 patients, type 3 in 11 patients, and type 4 in 13 patients. The mean follow-up periods were 48.7, 49.4, 18.4, and 38.0 months in type 1, 2, 3, and 4 patients, respectively (Table 1).

**Clinical Characteristics of Patients**

Risk factors such as age, sex, clinical diagnosis, occluded artery (ICA or MCA), hypertension, diabetes mellitus, prior myocardial infarction, hypercholesterolemia, and smoking were investigated (Table 1). There was no significant difference in these variables among the 4 groups.

**Risk of Recurrent Stroke During Follow-Up**

During the follow-up period, 16 total and 7 ipsilateral ischemic strokes occurred. There were no hemorrhages. The overall annual rate for total and ipsilateral stroke was 5.8% and 2.6%, respectively. In 39 type 1 patients, 6 total strokes and 1 ipsilateral ischemic stroke occurred 12 to 99 months after the initial ischemic attack. In 14 type 2 patients, 3 total strokes and 1 ipsilateral ischemic stroke occurred 2 to 93 months after initial ischemic attack. In 11 type 3 patients, there were 6 total and 4 ipsilateral ischemic strokes 5 to 31 months after onset. In 13 type 4 patients, there was 1 ipsilateral ischemic stroke 15 months after onset. Thus, the annual risks of subsequent total stroke were 3.8%, 5.2%, 35.6%, and 2.4% per year in type 1, 2, 3, and 4 patients, respectively. The annual risks of subsequent ipsilateral stroke were 0.6%, 1.7%, 23.7%, and 2.4% per year in type 1, 2, 3, and
4 patients, respectively. Fourteen deaths occurred in total: 3 in type 1, 4 in type 2, 4 in type 3, and 3 in type 4.

Because the annual risks of ipsilateral and total ischemic stroke in type 3 patients were distinctly higher than in other types of patients, we divided the 77 patients into 2 categories: 11 patients with decreased rCBF and rCVR (type 3) and 66 patients without (types 1, 2, and 4). Multivariate analysis with the Cox proportional-hazards model showed that having decreased rCBF and rCVR was a significant independent predictor of both ipsilateral and total stroke. No other risk factors were significant.

Kaplan-Meier analysis and Mantel-Cox log-rank statistics also showed that the risks of total and ipsilateral ischemic stroke in patients with decreased rCBF and rCVR (type 3) and 66 patients without (types 1, 2, and 4). Multivariate analysis with the Cox proportional-hazards model showed that having decreased rCBF and rCVR was a significant independent predictor of both ipsilateral and total stroke. No other risk factors were significant.

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Characteristics of Recurrent Strokes

Characteristics of recurrent stroke are summarized in Table 2. In type 1 and 2 patients, most ischemic strokes (66.7%) developed in the contralateral ICA or vertebrobasilar territories. In particular, progression of occlusive lesion in the contralateral ICA was closely related to stroke recurrence. In type 3 patients, all 4 ipsilateral strokes were indicated to result from hemodynamic failure because cerebral infarctions were seen in the MCA territory widely or in the watershed zones (Table 2).

Discussion

As described earlier, previous studies do not reach consistent conclusions about the impact of acetazolamide reactivity on prognosis (Table 3), probably because of analytical problems. Therefore, we designed the present study to avoid this problems. As a result, the present study demonstrated that patients with decreased rCBF and rCVR resulting from ICA or MCA occlusion have a higher risk of ipsilateral and total ischemic stroke than those without.

The results mirror the conclusion in the review article by Klijn et al. They reviewed previous studies on the outcome of medically treated patients with and without compromised rCBF. According to their meta-analysis, annual risks of total and ipsilateral stroke were 12.5% and 9.5%, respectively, in patients with disturbed reactivity to acetazolamide. Furthermore, they were much higher, 41.4% and 31.0%, in patients with severely impaired hemodynamic measurements. The prognosis for these patients was definitely worse than for those patients without compromised rCBF. The present study revealed that the relative risk conferred by type 3 ischemia (de-

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### TABLE 1. Clinical Characteristics of Patients Included in the Present Study

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>39</td>
<td>14</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.0±10.3</td>
<td>65.4±10.1</td>
<td>68.6±7.5</td>
<td>65.0±8.5</td>
</tr>
<tr>
<td>Sex, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosis, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>26</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>RIND</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Occluded artery, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>32</td>
<td>11</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>MCA</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Contralateral occlusive carotid lesion, n</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Xe133 SPECT results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBF, mL·100 g⁻¹·min⁻¹</td>
<td>42.0±2.4</td>
<td>40.8±3.0</td>
<td>34.8±3.6</td>
<td>36.0±4.2</td>
</tr>
<tr>
<td>rCVR, %</td>
<td>19.4±4.0</td>
<td>5.4±2.4</td>
<td>-5.4±4.8</td>
<td>20.0±5.2</td>
</tr>
</tbody>
</table>

| Risk factors, n  |          |          |          |          |
| Hypertension     | 28       | 10       | 8        | 6        |
| Diabetes mellitus| 12       | 4        | 4        | 5        |
| Prior myocardial infarction | 3 | 1 | 1 | 2 |
| Hypercholesterolemia | 10 | 3 | 3 | 3 |
| Smoking          | 22       | 7        | 6        | 5        |
| Mean follow-up, mo | 48.7 | 49.4 | 18.4 | 38.0 |
| Further total stroke, n | 6 | 3 | 6 | 1 |
| Further ipsilateral stroke, n | 1 | 1 | 4 | 1 |
| Annual risk of total stroke, % | 3.8 | 5.2 | 35.6 | 2.4 |
| Annual risk of ipsilateral stroke, %/y | 0.6 | 1.7 | 23.7 | 2.4 |

TIA indicates transient ischemic attack; RIND, reversible ischemic neurological deficits. Statistical values are shown as mean±SD.
creased rCBF and rCVR) was 8.0 (95% CI, 1.9 to 34.4) for ipsilateral stroke. This is very similar to previous results obtained from 2 PET studies. In those reports, the relative risk conferred by increased OEF was 6.4 (95% CI 1.6 to 26.1) or 7.3 (95% CI 1.6 to 33.4) for ipsilateral stroke.2,3

Acetazolamide has been widely used to assess cerebral perfusion reserve in patients with occlusive vascular disorder5–12,14 since Vorstrup et al5 reported its usefulness. Intravenous injection of acetazolamide is known to increase rCBF in a dose-dependent manner. Acetazolamide injection does not alter blood pressure and can estimate vasodilatory capacity, although CO2 inhalation may modify the result because of blood pressure augmentation.4,20 In previous studies,7,8 rCBF and rCVR were measured in 34 patients with ICA occlusion. All patients were classified into 4 types on the basis of 133Xe SPECT findings. In these preliminary studies, type 1 patients with normal rCBF and rCVR experienced no further stroke when treated medically for about 2 years. Cerebral angiography revealed well-developed collateral circulation through the anterior or posterior communicating artery in type 1 patients. Repeated SPECT studies also showed no significant changes in rCBF and rCVR during the follow-up periods. These results suggested that CPP is kept within a normal range in type 1 patients because of well-developed collateral circulation. In type 2 patients with normal rCBF and decreased rCVR, long-term normalization of rCVR was successfully obtained after STA-MCA anastomosis.7–9 Therefore, it is most likely that compensatory cerebral vasodilation occurs in response to a moderate reduction in CPP, decreasing rCVR, in type 2 patients. Such hemodynamic conditions may correspond to Powers’ stage I.22 Most type 3 patients with decreased rCBF and rCVR had contralateral ICA stenosis (>80%) or occlusion on cerebral angiography. A paradoxical rCBF decrease after acetazolamide injection is often observed in type 3 patients and is known as the steal phenomenon.4,7,8 Bypass surgery normalized rCVR in all patients. None suffered ischemic stroke during follow-up.7 These findings strongly indicated that autoregulatory vasodilation could no longer compensate for CPP reduction caused by inadequate collateral development, leading to a blood flow decline in type 3 patients. Therefore, type 3 ischemia may be a very similar condition to a state

TABLE 2. Clinical Characteristics of Patients Who Developed Stroke Recurrence

<table>
<thead>
<tr>
<th>Patient, n</th>
<th>Age, y</th>
<th>Sex</th>
<th>Occluded Artery</th>
<th>SPECT Type</th>
<th>Time to Stroke Recurrence, mo</th>
<th>Cerebral Infarct</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>MCA</td>
<td>1</td>
<td>99</td>
<td>Lacunar infarct</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>ICA</td>
<td>1</td>
<td>12</td>
<td>Lacunar infarct</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>M</td>
<td>ICA</td>
<td>1</td>
<td>16</td>
<td>MCA cortex</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>ICA</td>
<td>1</td>
<td>30</td>
<td>Cerebellum</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>M</td>
<td>ICA</td>
<td>1</td>
<td>13</td>
<td>MCA cortex</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>ICA</td>
<td>1</td>
<td>23</td>
<td>Pons</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>ICA</td>
<td>2</td>
<td>93</td>
<td>MCA cortex</td>
<td>Contralateral ICA stenosis progressed</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>ICA</td>
<td>2</td>
<td>26</td>
<td>Lacunar infarct</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>F</td>
<td>MCA</td>
<td>2</td>
<td>3</td>
<td>Watershed zone</td>
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<tr>
<td>10</td>
<td>76</td>
<td>M</td>
<td>ICA</td>
<td>3</td>
<td>24</td>
<td>MCA cortex</td>
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<td>11</td>
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<td>ICA</td>
<td>3</td>
<td>14</td>
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<tr>
<td>12</td>
<td>60</td>
<td>M</td>
<td>ICA</td>
<td>3</td>
<td>5</td>
<td>Thalamus</td>
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<tr>
<td>13</td>
<td>61</td>
<td>M</td>
<td>ICA</td>
<td>3</td>
<td>31</td>
<td>Cerebellum</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>76</td>
<td>M</td>
<td>ICA</td>
<td>3</td>
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<td>Watershed zone</td>
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<tr>
<td>15</td>
<td>66</td>
<td>F</td>
<td>ICA</td>
<td>3</td>
<td>5</td>
<td>Watershed zone</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>49</td>
<td>M</td>
<td>ICA</td>
<td>4</td>
<td>15</td>
<td>Lacunar infarct</td>
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</table>

VB indicates vertebrobasilar territory.
of misery perfusion or Powers’ stage II.11,22,23 No reports in the literature definitely document the pathophysiology of type 4 ischemia with decreased rCBF and normal rCVR. Bypass surgery could not improve blood flow, having no significant effects on cerebral hemodynamics. However, a recent study has indicated that selective neuronal injury resulting from long-lasting ischemia may be responsible for these results, although neither CT nor MRI could detect structural changes.24 It is most likely that metabolic demand is downregulated in response to a decreased blood flow in type 4 patients, although a precise PET study is necessary.

Recently, the prospective randomized clinical trial has been accepted as the highest level of evidence.25 In the present study, the included patients were graded on the basis of hemodynamic measurements when they were enrolled and were followed up monthly in an outpatient clinic. Therefore, this study is a prospective, longitudinal cohort study, although it lacks blinding during the follow-up period. The present study, however, also has some problems for evidence-based medicine. First, this study has bias in the patient selection. Although all patients diagnosed as types 1, 2, and 4 were included in this study, type 3 patients included in this study were not the whole population we experienced between 1990 and 1999 because the remainder of type 3 patients underwent STA-MCA anastomosis on the basis of our criteria (see above). As a result, the type 3 patients included in this study are a subgroup who did not consent to surgery, which might limit the ability to generalize from the conclusions. However, there was little investigator bias in deciding whether the patient should undergo surgery or not, and all type 3 patients included in this study were also followed up monthly. In addition, the overall annual rates of 5.8% and 2.6% for total and ipsilateral ischemic stroke in this study are comparable to those described previously. Thus, Kliijn et al21 reported that the annual rates of total and ipsilateral stroke were 5.5% (95% CI, 5.0 to 6.0) and 2.1% (95% CI, 1.6 to 2.8), respectively, in patients with symptomatic carotid occlusion. Therefore, we do not believe that the subjects in this study were eccentrically selected through some specific bias.

Second, the number of subjects (n=11) and outcome events (4 ipsilateral strokes) in type 3 was small. However, we do not believe that there are that many patients who are hemodynamically compromised because of occlusive carotid diseases. For example, Yamauchi et al3 recently reported that only 7 of 40 patients (17.5%) had increased OEF as a result of carotid occlusion, whereas another 33 patients (82.5%) had normal OEF. The follow-up period of type 3 subjects was also shorter than those of other patients because a significant number of type 3 subjects died of other diseases such as myocardial infarction. However, their number and follow-up period were sufficient for statistical analysis.

It should also be remembered that impaired vasodilatory capacity might improve during the follow-up period in a subgroup of patients.26,27 Widder et al26 reported that about half of the patients with ICA occlusion showed a spontaneous improvement of CO2 reactivity. Hasegawa et al26 reported improvement in acetazolamide reactivity in 5 of 20 patients. Spontaneous normalization of the ipsilateral-to-contralateral OEF ratio was also demonstrated in about half of the patients with ICA occlusion.27 These spontaneous improvements in vasodilatory capacity usually occur within a few months after onset. However, most of patients with bilateral ICA occlusion showed no significant change in vasodilatory capacity.26 The ipsilateral-to-contralateral OEF ratio remained high in 5 of 10 patients.27 Furthermore, Yamauchi et al28 recently reported that cerebral hemodynamics and metabolism may deteriorate during the follow-up period in patients with carotid occlusion. In addition, subsequent ipsilateral stroke is known to occur within a few months in hemodynamically compromised patients.1,2 These findings strongly suggest that hemodynamic parameters are still important factors for predicting outcome, although they may improve during follow-up in selected patients.

Previously, a large, international, randomized clinical trial on STA-MCA anastomosis conducted between 1977 and 1985 showed no beneficial effect in preventing recurrent ischemic stroke in patients with symptomatic carotid occlusion.29 However, as Grubb et al30 pointed out, the cerebral hemodynamic state of the enrolled patients was not previously measured. Nowadays, we can assess CPP reduction by determining OEF or rCVR to acetazolamide in patients with occlusive carotid diseases and should randomize a specific subgroup of patients with hemodynamic compromise in such clinical trials. In fact, although the annual rate for ipsilateral stroke exceeded 20% in type 3 patients when treated medically, it has been reported to be lower in similar patients after bypass surgery.7,9,30 Thus, Ishikawa et al30 reported that 4 of 28 patients experienced subsequent stroke during a mean follow-up of 48.9 months after STA-MCA anastomosis (annual rate, 3.5%). Now, an ongoing prospective randomized study in Japan, the Japanese EC/IC Bypass Study, is enrolling patients with reduced...
rCBF and rCVR to acetazolamide (type 3 according to our criteria) to clarify the beneficial effects of bypass surgery and is expected to provide more distinct answers on this subject.

In conclusion, the present results suggest that in this selected patient sample, reduced blood flow and reactivity to acetazolamide is predictive of subsequent ischemic stroke in patients with ICA or MCA occlusion. Quantitative measurements of blood flow and acetazolamide reactivity are very simple and useful for predicting patient outcome, although a prospective randomized trial is the next necessary step.

Acknowledgments

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References


Editorial Comment

There Is a Role for Cerebrovascular Reserve Testing

Although a role for embolic events as a cause of stroke is well established, the role of compromised hemodynamics remains unclear. Failure of superficial temporal to middle cerebral artery bypass surgery to significantly reduce the subsequent stroke rate in patients with symptomatic occlusive disease of the internal carotid artery or middle cerebral artery suggests
that the role of hemodynamics was either very small or nonexistent. Critics of the study suggest that the lack of benefit was due to the inclusion of patients who had no physiological indication for a procedure designed and proved to be capable of improving hemodynamics.

The study by Kuroda et al provides one more contribution to a body of literature supporting the concept of a subgroup of patients who have a chronically compromised blood supply and significantly increased stroke risk. The importance of this article is that it is the first prospective study that confirms the value of a test of cerebral vascular reserve (CVR) as a predictor of the high stroke risk subgroup.

The authors report the incidence of stroke in 77 patients with symptomatic carotid occlusion after the quantitative assessment of CVR. They used quantitative cerebral blood flow (CBF) measurements obtained with xenon 133 as the lipid-soluble tracer of CBF and single-photon emission CT (SPECT) for tomographic imaging. Studies were obtained immediately before and 20 minutes after an injection of acetazolamide, an agent known to increase CBF by inducing a local tissue acidosis. The "test-retest" format provided a means for isolating one variable, the ability of circulation to respond to a challenge that normally increases CBF by >30%. The assumption is that a lesser reactivity implies that the vascular bed is becoming increasingly vasodilated and thereby less able to vasodilate to the physiological challenge. A negative response ("steal phenomenon") has been associated with a dependence on ophthalmic and pial collaterals and implies a maximal vasodilatation.

Testing the validity of these assumptions, Kuroda et al reported that patients with a severely reduced CVR (mean of -5%) and a reduced baseline CBF had a significantly increased stroke risk (annual risk of 23.7%, with a relative risk of 8.0 for ipsilateral stroke). The authors suggest that the stroke incidence they observed, similar to that reported by Grubb et al (who used a measure of oxygen extraction fraction [OEF]), was due to their ability to distinguish the same subgroup of high-risk patients.

The suggestion that a study of CVR and a measure of oxygen extraction could identify a similar stroke subgroup is not surprising, based on examination of the underlying physiology presented in the seminal article by Powers et al. In that work, a series of stages of hemodynamic compromise were described. In stage 1, only blood volume is increased as perfusion pressure begins to fall and blood flow and oxygen availability remain uncompromised. Stage II is entered when a continuing drop of perfusion pressure occurs after a maximal vasodilation of precapillary vessels accompanied by a maximal blood volume. Within stage II, CBF falls from the norm of about 50 to near 20 mL/100 g per minute, without an apparent neurological deficit. Metabolism is maintained, despite the fall of CBF, by a rise of the OEF. A negative relationship between CVR by quantitative CBF and quantitative OEF has been reported. By combining a reduction of quantitative CBF with a severe compromise of CVR, especially the negative reactivity defined in the type

3 patients, the authors appear to have defined a group of patients that have a maximal CBV and a decrease of CBF who should have an elevated OEF.

Because OEF measurements are not only more costly but also less available, a CVR strategy for identifying patients at increased ischemic risk is desirable. If CVR proved to be as sensitive but less specific, it could function as a screening test before proceeding to a measure of OEF. If studies of CVR proved to be both sensitive and specific, they could be substituted for OEF. Other reasons to pursue a CVR strategy include the fact that OEF may be a less-reliable marker of ischemic risk after the subcortical white matter injuries that commonly accompany hemodynamic compromise. The currently proposed qualitative OEF measure also requires a "normal" hemisphere. It, therefore, cannot assess patients with bilateral disease, thus omitting the group at greatest ischemic risk with the most severe and prolonged hemodynamic disorder.

An important challenge will be to better define the advantages and disadvantages of the many approaches currently available for the measurement of both OEF and CVR.

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Long-Term Prognosis of Medically Treated Patients With Internal Carotid or Middle Cerebral Artery Occlusion: Can Acetazolamide Test Predict It?
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