Effect of Acetazolamide Reactivity and Long-term Outcome in Patients With Major Cerebral Artery Occlusive Diseases

Chiaki Yokota, MD; Yasuhiro Hasegawa, MD; Kazuo Minematsu, MD; Takenori Yamaguchi, MD

Background and Purpose—It remains unclear whether hemodynamic insufficiency plays a major role in ischemic events. We performed a prospective follow-up study in ischemic stroke patients with occlusive large-artery diseases to determine whether stroke recurrence is related to reduced vasodilatory capacity, judged with single-photon emission CT and acetazolamide (ACZ) challenge.

Methods—During the period from 1987 to 1995, we examined cerebral vasodilatory capacity with single-photon emission CT and an ACZ challenge in 105 consecutive stroke patients with severe stenosis (>75% in diameter) or occlusion of the internal carotid artery or the trunk of the middle cerebral artery who had no or minimal infarcts on CT. According to criteria reported earlier, the patients were divided into two groups: normal (negative ACZ, n=50) or reduced ACZ reactivity (positive ACZ, n=55). They were prospectively followed at regular intervals for a median period of 2.7 years.

Results—The Kaplan-Meier analysis revealed no difference in cumulative recurrence-free survival rate between the two groups. The multivariate analysis with Cox proportional hazards model demonstrated that a high systolic blood pressure at entry into the study significantly increased stroke recurrence (coefficient = .0466; hazard ratio = 1.0477; 95% confidence interval = 1.0017 to 1.0957; P = .04), whereas antihypertensive medication significantly reduced stroke recurrence (coefficient = −1.527; hazard ratio = 0.217; 95% confidence interval = 0.0612 to 0.771; P = .02), but no other variables including ACZ reactivity affected stroke recurrence rate.

Conclusions—The present results demonstrate that reduced vasodilatory capacity does not play a major role in stroke recurrence. Antihypertensive therapy appears to reduce stroke recurrence even in patients with hemodynamically significant arterial diseases. (Stroke. 1998;29:640–644.)

Key Words: acetazolamide • hemodynamics • tomography, emission computed • vasodilation

Brain infarction may occur in patients with severe stenosis or occlusion of proximal cerebral arteries and inadequate collateral blood supply when systemic perfusion is critically decreased by hypotension or bradycardia. This concept has led to several diagnostic and therapeutic attempts to identify a subgroup of patients at high risk for stroke and to increase blood flow supply to the hemodynamically compromised tissue. Powers et al, however, reported that PET evidence of abnormal cerebral hemodynamics did not identify such a subgroup. Their recent study again did not reveal a significant trend showing that patients with increased regional oxygen extraction fraction may be at high risk for stroke. An international randomized trial failed to demonstrate benefits of extracranial-intracranial arterial anastomosis to prevent recurrent strokes. Since these studies were reported, a question has arisen concerning the significance of chronic hemodynamic insufficiency on stroke occurrence.

In the report by Powers et al, PET studies were performed in only 30 patients and mainly within 30 days after stroke onset. The results were therefore inconclusive. Several recent studies demonstrated that patients with reduced or impaired vasodilatory capacity to ACZ or carbon dioxide may be at higher risk for subsequent stroke. Their conclusions, however, were compromised by unreliable methodologies, retrospective observations, or a small sample size.

We previously demonstrated that SPECT with [123I]IMP and an ACZ challenge can detect stage II hemodynamic failure with an elevation of oxygen extraction fraction as measured by simultaneous PET studies with the 15O-labeled gas inhalation method. We attempted to clarify the significant factors that govern stroke recurrence among several clinical variables, including vasodilatory capacity at entry into the study.

Subjects and Methods

Patient Entry

One hundred five patients (89 men, 16 women) who were admitted to our hospital (Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, Osaka, Japan) from September 1987 to June 1995 were prospectively enrolled in the present study. Their mean age was 63 years (range, 28 to 81 years).
Selected Abbreviations and Acronyms

ACZ = acetazolamide
AI = asymmetry index
CEA = carotid endarterectomy
ICA = internal carotid artery
$[^{123}I]$IMP = N-isopropyl-$p$-[${}^{123}$I]iodoamphetamine
FWHM = full width at half maximum
MCA = middle cerebral artery
PET = positron emission tomography
SPECT = single-photon emission computed tomography

The subjects were consecutive patients meeting the following criteria: (1) evidence of ischemic cerebrovascular events; (2) minimal infarct specified on CT, and (3) unilateral occlusion or severe stenosis (>75% in diameter) in the ICA or the trunk of the MCA confirmed by angiography with arterial catheterization. Patients were excluded from the study if they had (1) cardioembolic infarction according to our diagnostic criteria; (2) vascular lesions caused by other systemic diseases such as aortitis syndrome, moyamoya disease, or fibromuscular dysplasia; or (3) an occlusion or moderate to severe stenosis (>50%) of major cerebral arteries in the contralateral carotid or vertebrobasilar system.

SPECT Study

A SPECT study with ACZ challenge was performed in all patients later than 1 month after stroke onset. $[^{123}I]$IMP was used as a cerebral blood flow tracer with either of two gamma cameras: (1) a conventional rotating gamma camera (Starcam 400 AC/T; General Electric) with a 12-mm FWHM obtained from 64 projections and displayed on a 64×64 matrix, at sampling times of 20 to 30 seconds, with a general all-purpose collimator, or (2) a ring-type gamma camera (Headrome SET-070; Shimadzu) with an 8-mm FWHM obtained from a 20-minute acquisition onto a 128×128 matrix with a general all-purpose collimator. The second SPECT study was done with ACZ challenge 3 days after the baseline SPECT measurement. ACZ (1000 mg) was given intravenously 15 minutes before 4.5 mCi (166.5 MBq) of $[^{123}I]$IMP injection (Nihon MediPhysics). Data collection began 15 to 30 minutes after the tracer was injected, with patients supine with eyes covered for 15 minutes. Data were obtained from 64 projections and displayed on a 64×64 matrix, with each sampling time being 20 to 30 seconds. All data were corrected for an attenuation of 0.1/cm. The tomographic data were reconstructed with the use of a filtered back-projection algorithm. The FWHM of our SPECT equipment was approximately 2 cm within the image plane. Slice thickness was 6 mm.

SPECT Data Analysis

The method of SPECT data analysis was previously reported. An AI, the percentage of radioisotope activity of a region of interest in the ipsilateral MCA territory compared with that in the contralateral homologous region of interest, was used. We took regions of interest from the regression line of AI during an ACZ challenge (\(y = -3.98 + 1.03x\) (Baseline AI) – 3.98). This equation was obtained by means of the following equation: \(\Delta AI = AI \text{ During ACZ Challenge} - [1.03x (Baseline AI) - 3.98]\). This equation was obtained from the regression line of AI during an ACZ challenge (\(y\)) with baseline AI (\(x\)), \(y = -3.98 + 1.03x\) (\(r = .993\); \(P < .01\)), in 10 control patients (mean age, 62.7 years) without significant cerebral arterial lesions. Because we confirmed that \(\Delta AI\) has a normal distribution and the 95% confidence interval ranges from +8.4% to −8.4%, we diagnosed patients with \(\Delta AI\) of less than 8.4% as having reduced vasodilatory capacity.

Patient Evaluation and Outcome Measures

Based on the local cerebral blood flow reactivity to ACZ assessed by $[^{123}I]$IMP SPECT at entry into the study, patients were divided into either the ACZ-negative or -positive group, ie, normal and abnormally reduced vasodilatory capacity, respectively.

Risk factors at entry into the study such as age, sex, interviewed smoking status (daily consumption), blood pressure, fasting plasma glucose, glycosylated hemoglobin, total cholesterol, triglycerides, and HDL cholesterol levels were investigated. Neurological status examinations were performed every 1 or 2 years during the observation period. Blood pressure and the nature of medical treatment, including administration of antihypertensive, antplatelet, and anticoagulant medication, were also recorded at the outpatient clinic. Blood pressure during the observation period was obtained in the outpatient clinic by averaging three blood pressure values measured randomly at intervals of at least 6 months. Follow-up ACZ-SPECT studies were also performed if possible.

The mechanism of stroke recurrence was judged clinically. The carotid and vertebral arteries were examined by duplex ultrasonography in all patients with stroke recurrence. CT scan was also performed in all patients. Transcranial Doppler sonography, MR angiography, and cerebral angiography were performed if necessary. They were classified into the following categories: artery-to-artery embolism, hemodynamic, and unclassified mechanisms.

The present study was terminated on June 30, 1995. The primary end point was stroke recurrence. The observation was terminated when stroke recurred or patients died. Patients who underwent a surgical treatment such as extracranial-intracranial bypass and CEA during the follow-up period were dropped from the study on the date of surgery.

CEA was not considered for patients who were admitted between 1987 and 1991 because CEA was not a popular surgical treatment in Japan at that time. However, since 1991 the efficacy of CEA for preventing subsequent stroke has been clearly demonstrated by North American Symptomatic Carotid Endarterectomy Trial12 and European Carotid Surgery Trial13 studies. As a result, patients who present with clinical symptomatology that corresponds to the site of ICA stenosis (>75%) have typically undergone CEA, regardless of the result of the ACZ challenge test. Patients with inaccessible high-grade ICA stenosis or concomitant significant lesions with intracranial vascular systems and those who refused surgical treatment did not receive CEA despite the presence of symptomatic high-grade ICA stenosis.

The survival time for those without recurrence was considered the interval from the date of entry into the study to the date of the last visit before the study ended.

Statistical Analysis

To determine the differences of clinical backgrounds between the ACZ-positive and -negative groups, Student’s \(t\) test or the \(\chi^2\) test was used, as appropriate. A cumulative recurrence-free survival rate was compared between the two groups with the Kaplan-Meier method and log-rank statistics. A multivariate analysis with the Cox proportional hazards model was used to determine the joint effect of multiple variables on stroke recurrence over time. The risk factors, ACZ reactivity at entry into the study, and medical treatment during the observation period were considered covariates. The analyses were performed with the use of a commercial software package (SPSS 6.1, SPSS Inc). A value of \(P < .05\) was considered significant.

Results

One hundred five patients were enrolled in the study by June 1995. The median follow-up period from entry into the study to recurrence, death, or the last visit to the clinic was 32.5 months, with a range from 2 days to 7.8 years. Fifty-five patients had reduced vasodilatory capacity at entry into the study and were assigned to the ACZ-positive group (Table 1, Fig 1). The other 50 patients were assigned to the ACZ-negative group. The ACZ-positive group had higher systolic blood pressure at entry into the study than did the ACZ-negative group (\(P < .05\)). There was no significant difference in other variables between the two groups. The sites of vascular...
lesions were also comparable between the two groups (Table 1). Fifty-four patients were administered antihypertensive medication; 48 of them were administered a calcium antagonist, 14 an angiotensin-converting enzyme inhibitor, 5 a β-blocker, and 3 a diuretic as single or combined use. Eleven patients were taking both a calcium antagonist and an angiotensin-converting enzyme inhibitor. Ninety-three patients were administered antiplatelet agents, and only 3 were administered anticoagulant medication.

During the observation period, 13 patients had stroke recurrence, 11 died, 16 were treated surgically, and 11 dropped out of the study because they moved or for other reasons. Eight of the 13 recurrent patients had stenosis of the ICA or MCA at entry into the study. Two of the 8 patients with stenotic lesions at entry into the study progressed to occlusion at the time of recurrence. There was no evidence of progression in the other 6 patients. In the 16 patients who had surgical treatments, 9 underwent extracranial-intracranial bypass surgery (ACZ-positive in 6 and -negative in 3), and the other 7 had CEA (ACZ-negative in all). The outcome, as shown in Table 2, was comparable between the groups. Deaths were not caused by stroke but by cardiovascular events or neoplasms. The remaining 54 patients visited our outpatient clinic at regular intervals until the end of the study.

The mechanism of recurrent stroke was considered hemodynamic in 4 patients who had orthostatic hypotension or excessive antihypertensive medication just before the recurrence. Three of 4 patients with hemodynamic recurrence had reduced ACZ reactivity at entry into the study. Clinical investigation did not reveal the mechanism of recurrent stroke in the other 9 patients. Among them, three recurrent strokes were lacunar as judged by symptoms and CT findings.

Follow-up ACZ-SPECT studies were performed in 45 of those 54 patients. The ACZ reactivity became normal at intervals of 2 years on average (range, 0.7 to 5.2 years) in 11 of 24 patients with initially reduced ACZ reactivity. ACZ reactivity remained reduced in the other 13 patients. The other 9 patients who were enrolled in the study after June 1994 were not examined with repeated ACZ-SPECT studies.

There was no significant difference in cumulative recurrence-free survival rate between the ACZ-positive and -negative groups (Fig 2). When stroke recurrence and death were combined, no significant difference was again observed between the groups.

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>ACZ Positive</th>
<th>ACZ Negative</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>55</td>
<td>50</td>
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<tr>
<td>Age, y</td>
<td>63±9</td>
<td>62±10</td>
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<td>Smoking (+)</td>
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<td>No. of patients</td>
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<td>No. per day</td>
<td>26±16</td>
<td>29±16</td>
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<td>Fasting plasma glucose, mmol/L</td>
<td>6.82±1.2</td>
<td>6.27±2.0</td>
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<tr>
<td>HbA1c, %</td>
<td>5.4±1.2</td>
<td>5.3±1.1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.04±1.06</td>
<td>4.94±1.09</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.48±0.68</td>
<td>1.55±0.71</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.16±0.34</td>
<td>1.09±0.34</td>
</tr>
<tr>
<td>Systolic BP at entry, mm Hg</td>
<td>160±23</td>
<td>149±22*</td>
</tr>
<tr>
<td>Diastolic BP at entry, mm Hg</td>
<td>86±12</td>
<td>84±13</td>
</tr>
<tr>
<td>ICA (stenosed/occluded)</td>
<td>36 (12/24)</td>
<td>29 (21/8)</td>
</tr>
<tr>
<td>MCA (stenosed/occluded)</td>
<td>19 (9/10)</td>
<td>21 (10/11)</td>
</tr>
<tr>
<td>Follow-up period, mo</td>
<td>30.7±27.3</td>
<td>34.5±33.1</td>
</tr>
</tbody>
</table>

HbA1c indicates glycosylated hemoglobin; BP, blood pressure. Values are mean±SD.

*P<.05.

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**Table 2. Outcome**

<table>
<thead>
<tr>
<th></th>
<th>ACZ Positive</th>
<th>ACZ Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stroke recurrence</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Stroke recurrence</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Contralateral</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vertebrobasilar system</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Figure 1.** Representative images of an ACZ-positive patient as shown with ACZ challenge and [123I]IMP SPECT. Left, Before ACZ; right, after ACZ (1000 mg IV).

**Figure 2.** Kaplan-Meier analysis of the two ACZ groups. No significant difference was demonstrated in recurrence-free survival rate between the ACZ-positive and -negative groups (P=NS, log-rank test).
hemodynamic impairment among patients with transient ischemic attacks with severe carotid stenosis.\textsuperscript{2,3} Artery-to-artery embolism and progression of both large and small arteriopathy may be more common causes of recurrent stroke in a setting of arterial stenosis.

Follow-up ACZ-SPECT studies revealed that spontaneous normalization of impaired hemodynamics may not be a rare phenomenon.\textsuperscript{11,17} Widder et al\textsuperscript{18} demonstrated that cerebrovascular reactivity improved spontaneously with time in the majority of patients with carotid occlusions by transcranial Doppler sonography and CO$_2$ inhalation. We also reported that cerebral blood flow of the affected hemisphere in patients with atherothrombotic infarction increased spontaneously within 40 months of stroke.\textsuperscript{19} Development of collateral pathways, recanalization, or regression of atheroma may be the mechanism of these improvements.\textsuperscript{20,21}

Another explanation of why reduced ACZ reactivity does not play a significant role in predicting stroke recurrence is that the ACZ challenge test cannot detect patients with stage I hemodynamic failure.\textsuperscript{7} There may have been some patients with stage I hemodynamic failure in the ACZ-negative group.

Some might suspect that spontaneous normalization could not be distinguished from decreasing ACZ reactivity in the nonaffected hemisphere. Because a reduction in ACZ reactivity would occur in the occluded vascular territory, a heterogeneous cerebral blood flow distribution in ACZ-enhanced SPECT images should be observed in the nonaffected hemisphere. Such a heterogeneous cerebral blood flow distribution was not observed in our series.

Although a relationship between cerebral hemodynamics and stroke risk was not observed, high systolic blood pressure at entry into the study significantly elevated the hazard ratio of stroke recurrence. Because hypertension is the most important risk factor for atherosclerosis in major vessels and for small-vessel disease in penetrating arteries,\textsuperscript{22–24} antihypertensive therapy reduced stroke recurrence in this study.

Although hypertension is the major cause of stroke, as noted by Phillips and Whisnant,\textsuperscript{25} the effects of antihypertensive treatment on stroke survivors have not been established. In some case series, control of blood pressure reduced recurrent stroke.\textsuperscript{26,27} In contrast, no reduction in stroke recurrence was noted when hypertension was controlled in two population-based studies.\textsuperscript{28,29} Blood pressure reduction may increase the likelihood of a second event, since reduction of cerebral perfusion pressure might result in further cerebral ischemia and infarction. The J-curve phenomenon in stroke recurrence was documented in our previous study,\textsuperscript{30} as was the relation of diastolic blood pressure to the incidence of cardiac events.\textsuperscript{31,32} The J point, the nadir of the recurrence rate curve in relation to diastolic blood pressure, was higher in patients with atherothrombotic infarction than in patients with lacunar infarction.\textsuperscript{30}

Hemodynamically compromised brain tissues in some patients with atherothrombotic infarction are theoretically vulnerable to a decrease in systemic blood pressure. The blood pressure control level in the ACZ-positive group was higher than that in the negative group in the present study. In this study the attending physicians were not blinded to the findings of the ACZ challenge test. Blood pressure in the ACZ-positive group might have been controlled at a somewhat higher level than that in the ACZ-negative group to avoid hemodynamic crisis.

### Table 3. Risk Factors for Stroke Recurrence

<table>
<thead>
<tr>
<th>Variables</th>
<th>+</th>
<th>−</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67±7</td>
<td>61±10</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Smoking (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>No. per day</td>
<td>25±13</td>
<td>29±16</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>6.22±2.94</td>
<td>6.38±1.89</td>
<td>NS</td>
</tr>
<tr>
<td>HbA$_1c$, %</td>
<td>5.6±1.5</td>
<td>5.2±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.89±1.01</td>
<td>5.07±1.09</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.54±0.66</td>
<td>1.56±0.72</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.09±0.36</td>
<td>1.16±0.34</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>156±17</td>
<td>151±22</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>85±10</td>
<td>84±12</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>151±20</td>
<td>147±20</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82±15</td>
<td>81±11</td>
<td>NS</td>
</tr>
</tbody>
</table>

HbA$_1c$ indicates glycosylated hemoglobin; BP, blood pressure. Values are mean±SD.

* At entry into the study.
† During follow-up period.

Comparison of the baseline characteristics revealed that patients with recurrent stroke were older and had higher systolic blood pressure at entry into the study than the others (P<.05). Other variables had no significant effect on stroke recurrence (Table 3). The multivariate analysis with the Cox proportional hazards model demonstrated that a high systolic blood pressure at entry into the study significantly increased stroke recurrence (coefficient=-0.0466; hazard ratio=1.0477; 95% confidence interval=1.0017 to 1.0957; P=.04), whereas antihypertensive medication significantly reduced stroke recurrence (coefficient=-1.527; hazard ratio=0.217; 95% confidence interval=0.0612 to 0.771; P=.02). None of the other variables, including ACZ reactivity and antiplatelet medication, affected the stroke recurrence rate. Anticoagulant medication could not be included with the variables because of the small number of patients (n=3).

Of 55 ACZ-positive patients, 31 were administered antihypertensive medication during the observation period. Stroke recurred ipsilateral to the arterial stenosis/occlusion in ACZ-positive patients who were administered antihypertensive medication. Follow-up systolic blood pressure of this group was 154 mm Hg on average, which was the highest in all four groups.

### Discussion

The present study demonstrated that reduced ACZ reactivity determined with SPECT and ACZ challenge does not play a significant role in predicting stroke recurrence. The results did not agree with several recent reports that patients with impaired vasodilatory capacity may be at higher risk for subsequent stroke.\textsuperscript{3–8}

Only 4 patients were considered to have recurrence by a hemodynamic mechanism. Studies based on PET have not found evidence for selective hemodynamic impairment among
Stroke recurred ipsilateral to the arterial stenosis/occlusion in ACZ-positive patients who were given antihypertensive medication in the present study. If blood pressure was more aggressively reduced, recurrent stroke may have occurred more frequently in the ACZ-positive group.

In conclusion, reduced cerebral hemodynamic capacity does not play a major role in subsequent stroke in patients with cerebral artery occlusive disease. Artery-to-artery embolism or progression of vascular lesions may be more important in stroke recurrence. Treatment with antihypertensive drugs is safe and appears to reduce stroke recurrence if aggressive hypotensive therapy is avoided, particularly in patients with reduced vasodilatory capacity.

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References
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