Cerebrovascular Reactivity to Acetazolamide and Outcome in Patients With Symptomatic Internal Carotid or Middle Cerebral Artery Occlusion

A Xenon-133 Single-Photon Emission Computed Tomography Study

Kuniaki Ogasawara, MD; Akira Ogawa, MD; Takashi Yoshimoto, MD

Background and Purpose—The present study prospectively evaluated relationships among baseline characteristics, cerebral hemodynamics, and outcome of patients with symptomatic major cerebral artery occlusion, by quantitative measurement of cerebral blood flow using xenon-133 (133Xe) inhalation and single-photon emission computed tomography (SPECT).

Methods—Regional cerebrovascular reactivity (rCVR) to acetazolamide was calculated at entry to the study using 133Xe SPECT. Seventy consecutive patients aged less than 70 years with unilateral internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion were divided into 2 groups: normal or reduced rCVR, and prospectively followed up for a period of 24 months.

Results—During the follow-up period, recurrent strokes occurred in 8 of the 23 patients with reduced rCVR at entry and in 3 of 47 patients with normal rCVR. Cumulative recurrence-free survival rates in all patients, and in each subgroup of patients with ICA or MCA occlusion and reduced rCVR on entry, were significantly lower than in those with normal rCVR (P = 0.0030, P = 0.0404, and P = 0.0310, respectively; Kaplan-Meier analysis). Among the factors considered, only lower rCVR and resting regional cerebral blood flow values were significantly associated with the risk of stroke recurrence (P = 0.0019 and P = 0.0080, respectively; Cox regression multivariate analysis).

Conclusions—The present study demonstrated that reduced rCVR to acetazolamide as determined by 133Xe SPECT is significantly associated with an increased risk of stroke recurrence in patients with symptomatic MCA or ICA occlusion. (Stroke. 2002;33:1857-1862.)

Key Words: acetazolamide ■ cerebral artery occlusion ■ recurrence ■ tomography, emission computed

Major cerebral arterial occlusion or stenosis caused by atherosclerotic disease may lead to reduced perfusion pressure in the distal cerebral circulation. Reduced perfusion pressure (hemodynamic compromise) is suspected as a risk factor for ischemic stroke. The results of several previous studies have indicated that cerebral hemodynamic status can be predictive of the outcome of major cerebral arterial occlusive disease. In those studies, cerebral hemodynamic status was assessed using positron emission tomography (PET) or transcranial Doppler ultrasonography. Although PET enables measurement of cerebral blood flow (CBF) and oxygen metabolism, clinical availability is limited by cost and technical complexity. Cerebral perfusion and cerebrovascular reactivity have also been measured by transcranial Doppler ultrasonography, because normal cerebral artery blood flow velocity increases in response to vasodilatory stimuli such as CO2 inhalation or acetazolamide administration. However, approximately 10% of studies using transcranial Doppler ultrasonography fail to detect signals of cerebral artery blood flow because of poor insonation of the cranial window, and this method is essentially incapable of measuring cerebral perfusion distal to the lesion in patients with middle cerebral artery (MCA) occlusion. Recently, Klijn et al demonstrated that CO2 reactivity using transcranial Doppler ultrasonography did not predict recurrent cerebral ischemic events in symptomatic patients with carotid artery occlusion.

Single-photon emission computed tomography (SPECT) allows simple quantification of CBF and can detect hemodynamic compromise using acetazolamide challenge. Yokota et al have reported the only prospective study using SPECT and acetazolamide challenge that failed to find an association between hemodynamic failure and stroke risk. In...
that study, however, qualitative CBF was measured using N-isopropyl-p-\textsuperscript{[\text{123}]I}-iodoamphetamine (\textsuperscript{[\text{123}]IIMP}).\textsuperscript{23,24} The site most commonly involved with atherosclerosis is the origin of the internal carotid artery (ICA), followed by the MCA.\textsuperscript{25,26} Occlusion in the MCA is frequently associated with hemodynamic impairment in the distal cerebral circulation and in the ICA.\textsuperscript{27} However, no studies have systematically investigated the relationship between cerebral hemodynamics and subsequent risk of stroke in subgroups of patients with symptomatic MCA occlusion.

The present study prospectively evaluated relationships among baseline characteristics, cerebral hemodynamics, and outcomes in patients with symptomatic ICA or MCA occlusion, by quantifying CBF using xenon-133 (\textsuperscript{133}Xe) inhalation and SPECT.

**Subjects and Methods**

**Patient Entry**

Seventy patients (53 men, 17 women) who were admitted to Tohoku University Hospital from January 1993 to March 1996 were prospectively enrolled in the present study. The mean age was 57 (range, 38 to 69) years.

The subjects were consecutive patients meeting the following criteria: (1) age less than 70 years; (2) unilateral complete occlusion of the ICA or the horizontal portion of the MCA, as confirmed by angiography with arterial catheterization more than 1 month after the last ischemic event; (3) evidence of ischemic cerebrovascular events in the vascular territory of the MCA ipsilateral to the lesion within the 3 months before entering the study (patients with only ischemic eye symptoms, such as transient monocular blindness or retinal infarction, were not included); (4) useful residual function (modified Rankin disability scale\textsuperscript{28} 0, 1, or 2); (5) no or border zone infarction or lacunar infarction in the basal ganglia or deep white matter as determined by CT or MRI; and (6) written informed consent obtained from the patient or relatives. Patients were excluded from the study if they had the following: (1) cardioembolic eye symptoms according to the guidelines of the Cerebral Embolism Task Force,\textsuperscript{29} based on the onset profile, angiographic findings, and results of cardiovascular examinations such as electrocardiography and echocardiography; (2) vascular lesions caused by other systemic diseases such as aortitis syndrome, moyamoya disease, or fibromuscular dysplasia; (3) occlusion or moderate to severe stenosis (>50%) of major cerebral arteries in the contralateral carotid or vertebrobasilar system; or (4) poor systemic conditions such as cardiac failure, renal failure, hepatic failure, or diabetes mellitus (fasting blood sugar of 300 mg/dl or more), or severe hypertension (diastolic blood pressure of 110 mm Hg or more). The present study was approved by the local ethics committee.

**SPECT Methodology**

Regional CBF was determined using \textsuperscript{133}Xe inhalation and SPECT (HEADTOME SET-031; Shimadzu Co, Kyoto, Japan). The SPECT detector array consisted of 64 NaI crystals in a 38-cm diameter hemisphere. Projection data for dynamic imaging were processed using Butterworth-Ramachandran filters. A 6446 image matrix was used. Each patient underwent 2 rCBF measurements on the same day: (1) at rest (resting rCBF) and (2) after an intravenous injection of acetazolamide (acetazolamide challenge test). Patients inhaled acetazolamide (acetazolamide challenge test). Patients inhaled 1.48 GBq of \textsuperscript{133}Xe gas for 1 minute, and sequential SPECT imaging was performed every minute for 10 minutes using a high-sensitivity collimator. Quantitative CBF maps were reconstructed using the Kanno-Lassen method.\textsuperscript{30} Thirty minutes after the resting SPECT measurements, acetazolamide (1000 mg) was administered intravenously and 1.48 GBq of \textsuperscript{133}Xe gas was inhaled 10 minutes later.

The initial SPECT consisting of resting and acetazolamide challenge was performed in all patients more than 1 month after the last ischemic event, within the 3 days after cerebral angiography and within the 2 weeks before entry into the study. Follow-up SPECT using the same procedure and follow-up magnetic resonance angiography were performed 24 months after entry for all patients except for those who had died or developed recurrent strokes.

**SPECT Data Analysis**

We analyzed 1 tomographic plane located 50 to 75 mm above and parallel to the orbito-meatal line, corresponding to the levels from the basal ganglia to the body of the lateral ventricle. The region of interest (ROI) was directly positioned on the CBF images and neither CT nor MRI-SPECT imaging coregistration were used. An investigator blinded to the patient clinical data manually drew an irregular ROI of 16 cm\textsuperscript{2} or more in the cerebral cortex distributed by the isipsilateral MCA according to the atlas developed by Kretschmann and Weinrich.\textsuperscript{31} In patients with cortical infarcts in the ipsilateral MCA territory, the investigator made the ROIs smaller to adjust them to regions where no infarction was seen on CT and MRI. Regional cerebrovascular reactivity (rCVR) was calculated as follows: rCVR (%)=(\textsuperscript{[\text{133}]Xe} challenge CBF−resting rCBF)/ resting rCBF.\textsuperscript{31}

For \textsuperscript{133}Xe SPECT, we studied 10 normal individuals (8 men and 2 women aged 35 to 65 [mean, 52.3] years) to obtain normal control values before evaluation of CBF data in patients. Two hemispheres in each normal individual were examined, resulting in 20 ROIs. Normal values in these 20 ROIs ranged from 41.2 to 50.8 (mean±SD=46.1±3.7 mL/100 g · min; 95% CI=38.4 to 53.8 mL/100 g · min) for resting rCBF and from 22.5 to 34.0 (28.1±4.4%, 18.9 to 37.3%) for rCVR. Any value beyond the lower 95% confidence limits defined in normal subjects was considered reduced.

**Patient Management and Outcome Measures**

Based on the rCVR assessed by \textsuperscript{133}Xe SPECT at entry into the study, an investigator, blinded to patient clinical data, placed patients into either the normal or reduced rCVR group. Another investigator, blinded to SPECT results, assessed risk factors at entry into the study such as age, gender, complications (hypertension, diabetes mellitus, prior myocardial infarction, hypercholesterolemia), and smoking status.

All patients included in our study were treated with antiplalet therapy (81 mg/d of aspirin or 200 mg/d of ticlopidine HCl). Furthermore, the control of risk factors and use of other drugs was left to individual clinical judgment. None of the patients underwent bypass surgery. All patients were examined at our hospital at 1-month intervals by an investigator blinded to SPECT results and were followed up at 24 months after entry into the study. At each visit an interim history was obtained, and a neurological examination was performed.

The primary end points were stroke recurrence or death, and observations were terminated at this time. MRI or CT was obtained and compared with initial studies to confirm recurrent stroke. Stroke in previously symptomatic arterial territory without evidence of primary intracranial hemorrhage was classified as an ipsilateral ischemic stroke. The severity of recurrent stroke was assessed using the modified Rankin disability scale (score 0 to 2: minor stroke; 3 to 5: major stroke). This evaluation was performed at least 2 months after stroke.
### Results

Among the 70 patients included in the study, 38 had experienced transient ischemic attack and the remaining 32 had experienced minor completed stroke before entry to the study. Twenty-three patients were assigned to the reduced rCVR group, and the other 47 were assigned to the normal rCVR group (Table 1). No variables at entry to the study differed significantly between the 2 groups (Table 1).

All 70 patients were followed up for 2 years or until stroke recurrence or death. During the observation period, a total of 11 strokes were identified, of which 9 were ipsilateral to ICA or MCA occlusion. Strokes occurred in 8 of the 23 patients with reduced rCVR at entry and in 3 of the 47 patients with normal rCVR. All 8 strokes in the reduced rCVR group were ipsilateral, whereas 1 ipsilateral, 1 contralateral, and 1 vertebrobasilar stroke occurred in the normal rCVR group. Thus, the annual risks of subsequent stroke were 17.4% and 3.3% per year in the reduced rCVR and normal rCVR groups, respectively, and annual risks of subsequent ipsilateral stroke were 17.4% and 1.2% per year in the same groups. Major recurrent strokes developed in only 3 patients with reduced rCVR. One patient with normal rCVR died as a result of neoplastic disease. The cumulative recurrence-free survival rate in all patients with reduced rCVR at entry was significantly lower than in those with normal rCVR ($P=0.0404$ and $P=0.0310$, respectively; Figures 2 and 3).

Comparison of the baseline characteristics at entry for stroke recurrence is shown in Table 2. Multivariate analysis with the Cox proportional hazards model demonstrated that a low rCVR and a low resting rCBF at entry significantly increased stroke recurrence (hazard ratio, 0.924; 95% CI, 0.879 to 0.971; $P=0.0019$ for low rCVR; and hazard ratio, 0.861; 95% CI, 0.771 to 0.962; $P=0.0080$ for low resting rCBF). Other variables demonstrated no significant effect on stroke recurrence. Seven of 8 patients with ipsilateral stroke recurrence had both reduced rCVR and reduced resting rCBF at entry, whereas the remaining patient had normal rCVR and resting rCBF (Figure 4). No patients with a combination of reduced rCVR and normal resting rCBF, or normal rCVR and reduced resting rCBF, developed ipsilateral stroke recurrence.

Follow-up magnetic resonance angiography performed 24 months after entry demonstrated that no stroke recurrence-free survivors experienced spontaneous recanalization of the occluded ICA or MCA. With respect to interval changes of rCVR, irrespective of the site of occlusion, all 43 stroke recurrence-free survivors with normal rCVR at entry retained a normal rCVR at follow-up. The rCVR in 4 of the 9 stroke

### Statistical Analysis

Student’s $t$ test or the $\chi^2$ test determined differences in vascular risk factor profiles between the normal and reduced rCVR groups. A cumulative recurrence-free survival rate was compared between the 2 groups using the Kaplan-Meier method and log-rank statistics. Multivariate analysis using the Cox proportional hazards model determined the joint effect of multiple variables on stroke recurrence over time. Gender, age, site of vascular lesion, complications (hypertension, diabetes mellitus, prior myocardial infarction, hypercholesterolemia), smoking status, resting rCBF, and rCVR at entry were considered covariates. Statistical significance was set at the $P<0.05$ level.

### Table 1. Patient Characteristics With Respect to Regional CVR at Entry

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reduced (n=23)</th>
<th>Normal (n=47)</th>
<th>Total (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17 (74%)</td>
<td>36 (77%)</td>
<td>53</td>
</tr>
<tr>
<td>Age, yr (mean±SD)</td>
<td>57.3±7.3</td>
<td>56.5±8.9</td>
<td>56.8±8.3</td>
</tr>
<tr>
<td>Site of lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>14 (61%)</td>
<td>27 (57%)</td>
<td>41</td>
</tr>
<tr>
<td>MCA</td>
<td>9 (39%)</td>
<td>20 (43%)</td>
<td>29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (57%)</td>
<td>24 (51%)</td>
<td>37</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (35%)</td>
<td>13 (28%)</td>
<td>21</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2 (9%)</td>
<td>1 (2%)</td>
<td>3</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2 (9%)</td>
<td>2 (4%)</td>
<td>4</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (65%)</td>
<td>32 (68%)</td>
<td>47</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; rCVR, regional cerebrovascular reactivity; ICA, internal carotid artery; MCA, middle cerebral artery. Values are means±SD.

### Figure 1. Kaplan-Meier analysis of the 2 rCVR groups in all patients.

### Figure 2. Kaplan-Meier analysis of the 2 rCVR groups in patients with internal carotid artery (ICA) occlusion.
recurrence-free survivors with ICA occlusion and reduced rCVR at entry had returned to normal (18.9% or more) by follow-up. On the other hand, the rCVR did not normalize during follow-up in any of the 6 stroke recurrence-free survivors with MCA occlusion and reduced rCVR at entry.

**Discussion**

The present study demonstrated that reduced rCVR to acetazolamide determined using $^{133}$Xe SPECT is significantly associated with an increased risk of stroke recurrence in patients with symptomatic occlusion of the MCA or ICA. In addition, resting rCBF was found to predict recurrent stroke in patients with symptomatic occlusion of the MCA or ICA, although the parameter is not as strong a predictor as rCVR.

To prove that hemodynamic impairment is an independent risk factor for subsequent stroke, it is necessary to meet several criteria as presented by Derdeyn et al. The distinction between abnormal and normal cerebral hemodynamic status was clearly defined in the present study. In addition, this was a blinded, prospective study of 70 patients with symptomatic ICA or MCA occlusion. No patients were censored because of surgical revascularization or loss to follow-up, and the impact of risk factors was specifically assessed using multivariate analyses with the Cox proportional hazards model.

The present study included only patients with complete occlusion of the ICA or MCA and did not include those with stenosis, for 2 basic reasons. First, intracranial atherosclerotic stenoses are dynamic lesions. The degree of stenosis may progress or regress over the course of several months. When stenoses progress to occlusions in patients with blood flow to the distal circulation passing predominantly through such stenoses and inadequate collaterals, regional cerebral perfusion may be significantly altered. In this situation, cerebral circulation data at entry seem unlikely to predict the risk of further stroke. Second, major cerebral artery occlusive diseases may cause ischemic symptoms through both hemodynamic and embolic mechanisms. In particular, an ischemic event is most often caused in patients with atherosclerotic stenosis when emboli dislodge from that lesion. Therefore, we did not include patients with ICA or MCA stenosis in the present study, to avoid the complexities of embolic mechanisms as much as possible.

The hemodynamic effects of an occlusive lesion on the distal circulation have been categorized into 3 stages. Occlusive lesions often have no effect on the distal circulation (stage 0, normal cerebral hemodynamics). When the perfusion pressure distal to the lesion begins to fall, however, reflex vasodilatation maintains normal blood flow (stage 1). This response is known as autoregulation. Autoregulatory vasodilatation can be detected using 2 basic strategies. The first involves quantitative measurements of resting CBF and cerebral blood volume (CBV). CBV increases with autoregulatory vasodilatation and the CBV/CBF ratio, which is the vascular transit time of red blood cells, increases. The second method relies on measurements of CBF at rest and after a vasodilatory stimulus. An absent or diminished response indicates autoregulatory vasodilatation. When autoregulatory vasodilatation is not adequate to maintain normal CBF, CBF begins to fall. In this situation, the brain can increase the amount of oxygen it extracts from the blood (oxygen extrac-

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**TABLE 2. Risk Factors at Entry for Stroke Recurrence**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Stroke Recurrence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=11)</td>
<td>No (n=58)</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Age, yr</td>
<td>58.2±5.8</td>
<td>56.6±8.8</td>
</tr>
<tr>
<td>Site of lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>MCA</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>rCVR (%)</td>
<td>12.0±19.5</td>
<td>25.5±13.7</td>
</tr>
<tr>
<td>Resting regional CBF (mL/100 g · min)</td>
<td>31.9±4.8</td>
<td>34.8±7.4</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; other abbreviations are defined in Table 1. Values are means±SD.
tion fraction) to maintain normal cerebral oxygen metabolism. This stage (stage 2) of hemodynamic compromise has been termed “misery perfusion.” Although evidence indicates that patients with misery perfusion are at high risk of recurrent ischemic stroke, oxygen extraction fraction can be directly measured only by PET at present. On the other hand, diminished response to a vasodilatory stimulus accompanied by reduction in the resting CBF, which can be quantified by SPECT, theoretically indicates reduction of cerebral perfusion pressure below the lower limit of autoregulation, that is misery perfusion. Actually, in the present study, 7 of the 8 patients demonstrating ipsilateral stroke recurrence displayed both reduced rCVR and reduced resting rCBF at entry. Thus, these findings suggest that quantitative measurements of CBF using SPECT and acetazolamide challenge can detect misery perfusion and identify patients at high risk for ipsilateral stroke recurrence.

As described earlier, Yokota et al have reported a prospective study using qualitative assessment of acetazolamide reactivity by \[^{123}\text{I}]\text{IMP SPECT} that failed to find an association between hemodynamic failure and stroke risk. This is not consistent with our results. As Yonas et al indicated, qualitative assessment of acetazolamide reactivity by \[^{123}\text{I}]\text{IMP SPECT} is known to have low sensitivity and specificity for detecting patients with a compromised reserve. According to their report, the positive predictive value of the qualitative methods was 50%. Therefore, it is possible that patients were misclassified by qualitative analysis in regard to acetazolamide reactivity. On the other hand, using quantitative assessment of cerebrovascular reactivity to acetazolamide by the stable xenon-computed tomography technique, Webster et al demonstrated that hemodynamic failure in symptomatic patients with ICA stenosis or occlusion is an important predictor of subsequent ischemic stroke. Our result corresponded with their finding, although the methods used to quantify cerebral hemodynamics differed between these 2 studies.

All ipsilateral strokes in our patients with reduced rCVR occurred within 8 months of the last ischemic event before entry. These observations were consistent with previous findings that recurrent strokes in hemodynamically compromised hemispheres generally occur during the first 6 months after the onset of ischemic symptoms. Widder et al reported that patients who had experienced recent ischemic events demonstrated severely impaired cerebrovascular reactivity significantly more often than those with a remote ischemic event and that cerebral hemodynamics improved predominantly during the first few months after the ischemic event. Thus hemodynamic stroke is more likely to reoccur during the first few months after arterial occlusion in patients whose cerebrovascular hemodynamics remained impaired for this period. Optimal management such as avoiding excessive decreases in blood pressure and dehydration during this period may be essential in preventing recurrent stroke.

Evidence indicates that cerebrovascular reactivity spontaneously improves in approximately half of patients with unilateral ICA occlusion, predominantly during the first few months after the onset of ischemic symptom, provided no interval stroke occurs. In the present study, rCVR returned to normal levels at follow-up in 4 of the 9 stroke recurrence-free survivors with ICA occlusion and reduced rCVR at entry. This result was in accordance with previous findings. On the other hand, rCVR did not normalize during follow-up in any of the stroke recurrence-free survivors with MCA occlusion and reduced rCVR at entry. These findings suggest that cerebral hemodynamics impaired by MCA occlusion may remain in the long term, unlike those impaired by ICA occlusion. Spontaneous improvement of hemodynamic failure after major cerebral artery occlusion probably depends on the development of collateral circulation. Although collaterals across the circle of Willis and/or from the external carotid artery often perfuse an area distal to an occluded ICA, only pial or meningeal to pial collaterals are available to patients with MCA occlusion. Thus, the essentially inadequate development of collaterals to the distal circulation in MCA occlusion may result in longstanding hemodynamic failure. Also, in patients with carotid occlusion, Klijn et al have reported that the presence of leptomeningeal collateral pathways is associated with impaired cerebral hemodynamics and a high risk of recurrent cerebral ischemic events.

We concluded that although our patient cohort was quite limited, the risk of recurrent ischemic strokes was shown to be quite high in patients with symptomatic ICA or MCA occlusion and reduced rCVR. Cerebral hemodynamics may be improved by extracranial-intracranial (EC-IC) arterial bypass surgery. However, this procedure was not found to reduce the risk of subsequent stroke in patients with symptomatic major cerebral artery occlusive diseases in an international randomized trial conducted from 1977 to 1985. When that trial was conducted, subgroups of patients with key, relevant hemodynamic factors could not be reliably distinguished. However, more recent prospective studies have established means to identify these subgroups and the fact that they are at high risk for subsequent stroke when treated medically. Although EC-IC bypass surgery improves impaired cerebral hemodynamics, it may not benefit this subgroup of patients. However, because high-risk subgroups can now be more readily distinguished, new trials using EC-IC bypass surgery should be conducted in patients with symptomatic ICA or MCA occlusion and reduced cerebrovascular reactivity.

References


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