Silent Myocardial Ischemia in Patients With Symptomatic Intracranial Atherosclerosis

Associated Factors

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Background and Purpose—Optimization of coronary risk evaluation in stroke patients has been encouraged. The relationship between symptomatic intracranial atherosclerosis and occult coronary artery disease (CAD) has not been evaluated sufficiently. We aimed to investigate the prevalence of silent myocardial ischemia in patients with symptomatic intracranial atherosclerosis and to identify factors associated with its presence.

Methods—From 186 first-ever transient ischemic attack or ischemic stroke patients with intracranial stenoses, 65 fulfilled selection criteria, including angiographic confirmation of a symptomatic atherosclerotic stenosis and absence of known CAD. All patients underwent a maximal-stress myocardial perfusion single-photon emission computed tomography (SPECT). Lipoprotein(a) [Lp(a)], C-reactive protein, and homocysteine (Hcy) levels were determined before SPECT.

Results—Stress-rest SPECT detected reversible myocardial perfusion defects in 34 (52%) patients. Vascular risk factors associated with a pathologic SPECT were hypercholesterolemia (P = 0.045), presence of >2 risk factors (P = 0.004) and high Lp(a) (P = 0.023) and Hcy levels (P = 0.018). Ninety percent of patients with high Lp(a) and Hcy levels had a positive SPECT. Existence of a stenosed intracranial internal carotid artery (ICA; odds ratio [OR], 7.22; 2.07 to 25.23; P = 0.002) and location of the symptomatic stenosis in vertebrobasilar arteries (OR, 4.89, 1.19 to 20.12; P = 0.027) were independently associated with silent myocardial ischemia after adjustment by age, sex, and risk factors.

Conclusions—More than 50% of the patients with symptomatic intracranial atherosclerosis and not overt CAD show myocardial perfusion defects on stress-rest SPECT. Stenosed intracranial ICA, symptomatic vertebrobasilar stenosis and presence of high Lp(a) and Hcy levels may characterize the patients at a higher risk for occult CAD.

Key Words: coronary artery disease ■ homocysteine ■ intracranial atherosclerosis ■ tomography, emission computed, single-photon

Coronary artery disease (CAD) is a frequent cause of death among stroke survivors.1 Recently appeared guidelines encourage healthcare professionals to optimize coronary risk evaluation in patients with transient ischemic attack (TIA) and ischemic stroke to establish appropriate strategies to prevent incident CAD.2 Moreover, ischemic stroke and TIA represent the common final expression of different cerebrovascular diseases, and those stroke subtypes related to underlying atherosclerosis may imply a higher risk of harboring asymptomatic CAD than other causes of stroke.3 Intracranial atherosclerosis is a major cause of stroke worldwide.4,5 A significant proportion of patients affected by this condition may develop incident CAD within the following few years, often with fatal consequences.6,7 Although previous studies have demonstrated the high prevalence (25% to 60%) of asymptomatic CAD in patients with symptomatic extracranial internal carotid artery (ICA) atherosclerosis,8,9 the relationship between symptomatic intracranial atherosclerosis and occult CAD has not been evaluated sufficiently.

The aims of the present study were to investigate the prevalence of silent myocardial ischemia in patients with symptomatic intracranial atherosclerosis without known CAD and to identify factors associated with its presence. For the second purpose, we focused on the role of traditional and novel risk factors such as lipoprotein(a) [Lp(a)], homocysteine (Hcy), and C-reactive protein (CRP) and on the potential impact of the distribution of intracranial atherosclerotic stenoses.

Subjects and Methods

Patient Selection

Our target group consisted of patients with a first-ever TIA or nondisabling ischemic stroke attributable to angiographically con-
firmed intracranial atherosclerotic stenoses, without documented history or diagnosis of CAD. A total of 186 first-ever TIA or ischemic stroke patients with symptomatic intracranial stenosis detected by transcranial Doppler (TCD) were admitted to our stroke unit. Overt CAD was defined as the presence of angina or clinical equivalents or history or electrocardiographic signs of previous myocardial infarction. To rule out symptomatic CAD, review of the medical history, electrocardiographic analysis, and cardiological anamnesis, including an angina questionnaire, were conducted. Reasons for exclusion of potential candidates after complete diagnostic work-up were: age >75 years (n = 25); modified Rankin Scale (mRS) score >2 (n = 20); symptomatic CAD (n = 18); embolicengenic cardiopathy (n = 21); TIA or stroke related to cervical ICA stenosis (n = 10); absence of confirmation of intracranial stenoses with magnetic resonance angiography (MRA) or computed tomography angiography (CTA); n = 9; nonatherosclerotic causes of intracranial stenosis (n = 10); neoplasm (n = 4); chronic inflammatory conditions (n = 3); and denial of informed consent (n = 1). Our diagnostic protocol to rule out nonatherosclerotic causes of intracranial stenoses, including an immunological study, has been reported in detail. Finally, 65 patients were included in the study. At inclusion visit performed 3 to 6 months after the qualifying event, informed consent and blood samples were obtained from all patients. Myocardial perfusion single-photon emission computed tomography (SPECT) was performed within 6 weeks thereafter. This study was approved by the local ethics committee.

Ultrasound Protocol
TCD recordings were performed using a Multi-Dop-X/TC Or (Dol Elektronische Systeme) device, with a hand-held transducer in a range-gated, pulsed-wave mode at a frequency of 2 MHz. We used a standard method of insonation through the temporal, occipital, and orbital windows without compression testing, as described previously. Intracranial stenoses were diagnosed according to validated criteria. Cervical ICA atherosclerosis was defined as present when any of the ICAs showed a >30% asymptomatic stenosis and categorized mild if one or both ICAs had a mild <50% stenosis; moderate when any of the ICAs presented a moderate <70% stenosis; and severe if any ICA had a severe asymptomatic stenosis.

MRA and CTA
Intracranial stenoses were confirmed during admission by MRA or by CTA, when it was not possible to perform MRI. Our MRA and CTA protocols have been described in detail previously. Intracranial stenosis was defined as a focal narrowing >50% in luminal reduction affecting the main cerebral large arteries.

Vascular Risk Factors and Clinical Variables
Cigarette smoking and medical history of hypertension, hypercholesterolemia, and diabetes mellitus were recorded at the inclusion visit. Body mass index was calculated by the formula kg/m². Treatment was allocated after the stenoses were confirmed following the criteria of the neurologist in charge. Use of acenocoumarol, aspirin, clopidogrel, statins, ß-blockers, calcium antagonists, nitrates, and angiotensin-converting enzyme inhibitors was registered. Functional status at day 90 was assessed by means of mRS. An mRS score =2 was considered indicative of functional independence.

Lp(a), Hcy, and CRP Determination
Blood samples were drawn at the inclusion visit always after overnight fast. Conditions known to modify CRP, Lp(a), or Hcy levels were ruled out before sampling. One of the evacuated tubes was immediately immersed in ice water up to the neck and transported to the laboratory at 0°C for Hcy determination. After centrifugation at 3500 rpm and 4°C for 15 minutes, plasma Hcy concentration was calculated by fluorescence polarization immunooxanalysis (Axis Biomedica) and expressed in micromoles per liter, whereas serum was blind-coded and stored at ~80°C until used. Serum Lp(a) concentration was determined by a commercially available enzyme-linked immunoassay (Macoa; Trinity Biotech) and expressed in milligrams per deciliter. High-sensitivity CRP serum level was measured with a Behringer nephelometer analyzer and expressed in milligrams per liter. All determinations were done by duplicate. The mean intra-assay coefficients of variation were <10% in all cases.

Myocardial Perfusion SPECT Protocol
Exercise Test
All patients performed a symptom-limited exercise test on a bicycle ergometer with the patient in the sitting position. Before exercise testing, a clinical evaluation was conducted by a cardiologist, who confirmed the absence of cardiac symptoms. The initial workload was 50 W, with 25-W increments every 3 minutes until exhaustion, appearance of anginal symptoms, hypotension or ST-segment depression >2 mm. When the peak heart rate was <80% of the maximal predicted value and oxygen consumption was <5 metabolic equivalents without angina or ECG changes, dipyridamole was administered intravenously at a rate of 0.14 mg/kg per minute for 4 minutes while the patient continued to exercise at the maximal tolerated load until 2 minutes after the end of the drug administration. Dipyridamole was interrupted if the patient developed angina or ≥1 mm ST-segment depression.

Myocardial Stress 99mTc-Methoxyisobutylisonitrile SPECT
All patients received an intravenous dose of 99mTc-methoxyisobutylisonitrile (MBI; 8 mCi) 30 to 60 seconds before the end of exercise. Stress images were acquired with a scintillation camera with a high-resolution collimator and a semicircular orbit 15 to 30 minutes after the administration of the radiopharmaceutical. A 24-mCi dose of 99mTc-MBI was administered immediately after stress images were obtained, and rest images were obtained 60 to 90 minutes thereafter. Reconstruction was performed, and short-axis, horizontal long-axis, and vertical long-axis sections were obtained. Myocardium was divided into 17 segments following current guidelines. A segment was considered ischemic if a mild, moderate, or severe exercise perfusion defect was reversible at rest images. SPECT studies were considered pathologic only when a perfusion defect was present in stress images in at least 2 of the 3 axes or in 3 consecutive tomographic sections on the same axis. Each study was reviewed independently by 2 investigators who were blinded to clinical and biochemical data. Following this protocol, reported sensitivity and specificity values of myocardial SPECT to detect significant CAD compared with coronary angiography at our institution are 93% and 94%, respectively, for those patients who do not require dipyridamole administration, and 89% and 86%, respectively, in the dipyridamole group.

Statistical Analysis
Statistical analyses were made by use of SPSS statistical package version 9.0. Statistical significance for intergroup differences was assessed by the χ² test for categorical variables and the t Student Mann–Whitney U and Kruskal–Wallis tests for continuous variables. Lp(a), CRP, and Hcy were not normally distributed (Kolmogorov–Smirnov). To study the relationship between Lp(a), CRP, and Hcy levels and a pathologic SPECT, receiver operator characteristic (ROC) curves were configured, and optimal cutoff values were used to dichotomize the variables to include them into the multivariate analyses. Multiple logistic regression models were performed to detect factors independently associated with the presence of silent myocardial ischemia, in which variables showing a P <0.1 on univariate testing were included, and adjustment by age, sex, hypertension, diabetes, hypercholesterolemia, and smoking was conducted. Finally, age-, sex-, and vascular risk factor–adjusted odds ratios (ORs) for a pathologic SPECT associated with the presence of a stenosis in each cerebral large artery were computed. Results were expressed as adjusted OR and corresponding 95% CIs. A P value <0.05 was considered significant.
TABLE 1. Demographic Data, Risk Factor Profile, and Clinical Characteristics of the Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>64.7±8.2</td>
</tr>
<tr>
<td>Sex (female), no. (%)</td>
<td>19 (29.2)</td>
</tr>
<tr>
<td>Vascular risk factors, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (73.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31 (47.7)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>51 (78.5)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>34 (52.3)</td>
</tr>
<tr>
<td>&gt;2 vascular risk factors</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>27.3±4.3</td>
</tr>
</tbody>
</table>

Qualifying event

<table>
<thead>
<tr>
<th>Event</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Cerebral infarction/TIA (%)</td>
<td>43 (66.2/22 (33.8)</td>
</tr>
<tr>
<td>Third-month mRS score (n)</td>
<td>0 (49/1 (14)/2 (5)</td>
</tr>
<tr>
<td>Serum level, median (Q1–Q3)</td>
<td></td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>17 (5–31)</td>
</tr>
<tr>
<td>Hcy, µmol/L</td>
<td>11.6 (9.9–14.8)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>2.5 (1.5–6.5)</td>
</tr>
</tbody>
</table>

Q1–Q3 indicates interquartile range 1 through 3.

Results

Descriptive Analysis

Vascular risk factor profile and demographic and clinical characteristics of the study group are shown in Table 1. The qualifying ischemic event was an ischemic stroke in 43 (66%) patients and TIA in the remaining 22 (34%). The responsible intracranial stenoses were located as follows: in intracranial ICA in 15 patients, in the middle cerebral artery (MCA) in 26 cases, in the posterior cerebral artery in 5, and in the vertebrobasilar arteries in 12 patients. In the remaining 7 patients, it was not possible to discriminate which stenosis had been symptomatic.

Intracranial stenoses were confirmed by MRA in 57 (88%) patients and by CTA in the remaining 8. A total of 175 stenoses were identified and distributed as follows: 53 (30%) in intracranial ICA, 56 (32%) in MCA, 6 (3%) in anterior cerebral artery, 36 (21%) in posterior cerebral artery, and 24 (14%) in the vertebrobasilar arteries. The median number of stenoses per patient was 2, ranging from 1 stenosis in 10 patients to 8 in 1. Coexistent asymptomatic extracranial ICA atherosclerosis was present in 24 (37%) patients, categorized in mild in 4 cases, moderate in 6, and severe in 14 patients.

Median levels of Lp(a), CRP, and Hcy are also shown in Table 1. There were no differences in the concentrations of these molecules regarding stroke severity, clinical presentation, and treatment groups. Hcy level was higher in men (P=0.028).

None of the selected patients had ever consulted a cardiologist. Before SPECT performance, none of them had presented angina or other cardiac symptoms. All patients were on sinus rhythm.

Myocardial Perfusion Stress-Rest

99mTc-MIBI SPECT

The peak heart rate during exercise stress testing was 116±16 bpm, the maximal systolic blood pressure was 182±28 mm Hg, and the peak oxygen consumption was 5.4±1.1 metabolic equivalents. Dipyridamole was administered to 27 (41%) patients with an optimal clinical tolerance. By the time of test performance, 5 (8%) patients were receiving β-blockers and 8 (12%) calcium antagonists. Three (5%) patients had angina during the test and 13 (20%) developed an ST-segment depression >1 mm.

Thirty-four (52%) patients showed scintigraphic myocardial ischemia. Main location and severity of the myocardial perfusion defects on SPECT images were as follows: 9 (26%) patients showed anterior, septal, or apical defects, of which 4 were considered mild, 3 moderate, and 2 severe; and 25 (74%) patients had inferior or lateral perfusion defects, of which 8 were mild, 9 moderate, and 8 severe. Until the moment this manuscript was submitted, 3 patients with a positive SPECT had undergone a coronary angiography, which confirmed significant CAD in all of them.

Traditional and Novel Vascular Risk Factors and Scintigraphic Myocardial Ischemia

Table 2 shows the results of the univariate analysis of vascular risk factors potentially associated with a pathologic myocardial perfusion SPECT. Hypercholesterolemia (P=0.045) and presence of >2 traditional risk factors for atherosclerosis (P=0.004) were significantly associated with a positive SPECT. Significant ROC curves were obtained for Lp(a) and Hcy, and the optimal cutoff points were Lp(a) >17 mg/dL (66% sensitivity, 63% specificity) and Hcy >12.4 µmol/L (62% sensitivity, 70% specificity). Patients with Lp(a) (P=0.023) and Hcy levels (P=0.018) above these values had a higher probability of ischemic heart disease. Figure 1 illustrates how the probability of showing myocardial perfusion defects reaches its maximum (90%) in patients with high Lp(a) and Hcy levels. A multiple logistic regression model revealed that Hcy >17 mg/dL (OR, 3.69, 1.06 to 12.84; P=0.04) and presence of >2 risk factors (OR, 5.1, 1.47 to 17.63; P=0.01) were independently associated with scintigraphic myocardial ischemia after adjustment by age, sex, and risk factors.

Distribution of Intracranial Atherosclerosis and Abnormal Myocardial Perfusion SPECT

We first analyzed the influence of the distribution of intracranial stenoses, either symptomatic or not, on the probability of a pathologic SPECT. Adjusted ORs for atherosclerosis (P=0.004) and presence of >2 risk factors (OR, 5.1, 1.47 to 17.63; P=0.01) were independently associated with scintigraphic myocardial ischemia after adjustment by age, sex, and risk factors.
risk (100%) was observed for those patients with a symptomatic vertebrobasilar stenosis and a coexistent asymptomatic intracranial ICA stenosis.

Regarding the extent of intracranial atherosclerosis, patients with multiple stenoses had a higher probability of showing scintigraphic ischemia than those with a single stenosis ($P=0.026$). Furthermore, the prevalence of occult CAD in patients with coexistent extracranial ICA stenoses was 62.5%. However, neither the presence nor the severity of cervical ICA atherosclerosis was significantly associated with a higher risk for a pathologic myocardial perfusion SPECT, as shown in Table 2.

**Discussion**

Noninvasive screening for asymptomatic CAD in all patients with cerebrovascular disease may not be cost-effective, and therefore, evidence to optimize coronary risk evaluation in TIA and stroke patients may be needed. The major finding of our study is that patients with TIA or ischemic stroke attributable to intracranial atherosclerotic stenosis have a high prevalence (52%) of abnormal myocardial perfusion SPECT studies, suggesting occult CAD. In addition, we were able to identify factors that may help discriminate which patients with symptomatic intracranial atherosclerosis are at a higher risk of harboring not overt CAD: existence of a stenosed intracranial ICA, location of the symptomatic stenosis in the vertebrobasilar arteries, and presence of high levels of Lp(a) and Hcy.

Intracranial atherosclerosis is a major cause of stroke worldwide. In the last decades, a growing concern about the coronary risk in patients with TIA or ischemic stroke has emerged. Previous studies showed that the frequency of asymptomatic CAD in unselected stroke patients is around

**TABLE 2. Relationship Between Vascular Risk Factors and Silent Myocardial Ischemia**

<table>
<thead>
<tr>
<th></th>
<th>Normal SPECT (n=31)</th>
<th>Pathologic SPECT (n=34)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years±SD</td>
<td>63.7±7.4</td>
<td>65.6±8.8</td>
<td>0.357</td>
</tr>
<tr>
<td>Sex (male), no. (%)</td>
<td>19 (61.3)</td>
<td>27 (71.4)</td>
<td>0.109</td>
</tr>
<tr>
<td>Hypertensive, no. (%)</td>
<td>24 (77.4)</td>
<td>24 (70.6)</td>
<td>0.531</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>12 (38.7)</td>
<td>19 (65.9)</td>
<td>0.166</td>
</tr>
<tr>
<td>Hypercholesterolemia, no. (%)</td>
<td>21 (67.7)</td>
<td>30 (88.2)</td>
<td>0.045</td>
</tr>
<tr>
<td>Cigarette smoking, no. (%)</td>
<td>14 (45.2)</td>
<td>20 (58.8)</td>
<td>0.271</td>
</tr>
<tr>
<td>&gt;2 risk factors, no. (%)</td>
<td>10 (32.3)</td>
<td>23 (67.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>27.3±4.9</td>
<td>27.5±3.8</td>
<td>0.825</td>
</tr>
<tr>
<td>Presence of cervical ICA atherosclerosis, no. (%)</td>
<td>9 (29)</td>
<td>15 (44.1)</td>
<td>0.208</td>
</tr>
<tr>
<td>Lp(a) &gt;17 mg/dL, no. (%)</td>
<td>11 (36.7)</td>
<td>21 (65.6)</td>
<td>0.023</td>
</tr>
<tr>
<td>Hcy &gt;12.4 μmol/L, no. (%)</td>
<td>9 (30)</td>
<td>16 (45.9)</td>
<td>0.018</td>
</tr>
<tr>
<td>HeS-CRP g/L, median (Q1–Q3)</td>
<td>2.3 (1.3–7.4)</td>
<td>2.6 (1.7–5.9)</td>
<td>0.830</td>
</tr>
</tbody>
</table>

The table resumes the results of the univariate analysis of traditional and new vascular risk factors potentially associated with the presence of silent myocardial ischemia. Results of multivariate analysis are shown in text.

Q1–Q3 indicates interquartile range 1 through 3; hsCRP, high-sensitivity CRP.

**TABLE 3. Multivariable Adjusted ORs for a Pathologic SPECT by Diseased Intracranial Large Artery**

<table>
<thead>
<tr>
<th>Stenosed Artery</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial ICA</td>
<td>7.22</td>
<td>2.07–25.23</td>
<td>0.002</td>
</tr>
<tr>
<td>MCA</td>
<td>0.37</td>
<td>0.11–1.24</td>
<td>0.106</td>
</tr>
<tr>
<td>PCA</td>
<td>1.72</td>
<td>0.55–5.36</td>
<td>0.348</td>
</tr>
<tr>
<td>Vertebrobasilar</td>
<td>1.16</td>
<td>0.35–3.82</td>
<td>0.805</td>
</tr>
</tbody>
</table>

ORs adjusted by age, sex, hypertension, diabetes, hypercholesterolemia, and smoking for the presence of scintigraphic myocardial ischemia.

PCA indicates posterior cerebral artery.
Moreover, the prevalence of occult CAD may be higher in patients with large-vessel atherothrombotic disease. However, most studies performed in this group of patients have been restricted to extracranial ICA atherosclerosis. We performed for the first time a systematic evaluation of myocardial perfusion in patients with first-ever symptomatic intracranial atherosclerotic stenosis in absence of diagnosed CAD. Our study demonstrates that the prevalence of occult CAD in these patients (52%) is as high as the one reported in patients with symptomatic cervical ICA stenosis.

As expected, the risk of asymptomatic CAD was higher in patients exposed to >2 traditional risk factors for atherosclerosis. More remarkable is the predictive role observed for Hcy and Lp(a) levels. When considered separately, only Hcy added relevant prognostic information to the one provided by conventional risk factors, but the combination of high levels of both molecules was a powerful independent marker of a pathologic myocardial perfusion SPECT. Both Hcy and Lp(a) have been shown to be risk factors for CAD and may directly promote atheroma development through several basic mechanisms. Further prospective studies are needed to elucidate whether, beyond their utility as markers of an increased risk for occult CAD, Hcy and Lp(a) may be suitable targets for preventive therapies.

The results of our study support the notion that atherosclerosis is a systemic disease. However, the atherosclerotic process may have peculiar characteristics in each arterial territory. In this setting, we found an interesting association between the distribution of intracranial atherosclerosis and the probability of scintigraphic myocardial ischemia. The location of the symptomatic stenosis in the vertebral or basilar arteries and the existence of a diseased intracranial ICA were independent markers of a pathologic myocardial perfusion SPECT. We suggest that this pattern of distribution of intracranial stenoses may serve as an indicator of a generalized atherosclerotic disease.

This study may have implications for the comprehensive management of patients with symptomatic intracranial atherosclerosis. First, to optimize coronary risk evaluation, we suggest that noninvasive coronary testing may be required for those intracranial atherosclerosis patients who present factors associated with a high risk for occult CAD. Second, regarding dietary and lifestyle modifications, risk factor control, and use of statins, patients affected by this condition may need to be considered as having an equivalent for CAD. Third, the choice of antithrombotic therapy for the secondary prevention of patients with symptomatic intracranial stenoses without known history of CAD should take into account the high likelihood of harboring asymptomatic CAD, and antiplatelet agents may be preferable to oral anticoagulants. And fourth, patients with abnormal provocative tests for myocardial ischemia may need to be referred to a cardiologist for further evaluation because of the increased risk for cardiac events.

In this context, there is no established consensus on the appropriate treatment of asymptomatic CAD in cerebrovascular patients. Finally, future research should be aimed to establish the most adequate preventive strategies to improve cardiac outcome in patients affected by symptomatic intracranial atherosclerosis.

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