Progressive Cortical Neuronal Damage and Chronic Hemodynamic Impairment in Atherosclerotic Major Cerebral Artery Disease

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Background and Purpose—Cross-sectional studies suggest that chronic hemodynamic impairment may cause selective cortical neuronal damage in patients with atherosclerotic internal carotid artery or middle cerebral artery occlusive disease. The purpose of this longitudinal study was to determine whether the progression of cortical neuronal damage, evaluated as a decrease in central benzodiazepine receptors (BZR), is associated with hemodynamic impairment at baseline or hemodynamic deterioration during follow-up.

Methods—We evaluated the distribution of BZR in 40 patients using positron emission tomography and 11C-flumazenil over time in 80 medically treated patients with atherosclerotic internal carotid artery or middle cerebral artery occlusive disease that had no ischemic episodes during follow-up. Using 3D stereotactic surface projections, we quantified abnormal decreases in the BZRs in the cerebral cortex within the middle cerebral artery distribution and correlated changes in the BZR index with the mean hemispheric values of hemodynamic parameters obtained from 15O gas positron emission tomography.

Results—In the hemisphere affected by arterial disease, the BZR index in 40 patients (50%) was increased during follow-up (mean 26±20 months). In multivariable logistic regression analyses, increases in the BZR index were associated with the decreased cerebral blood flow at baseline and an increased oxygen extraction fraction during follow-up. Increases in the oxygen extraction fraction during follow-up were associated with a lack of statin use.

Conclusions—In patients with atherosclerotic internal carotid artery or middle cerebral artery disease, the progression of cortical neuronal damage was associated with hemodynamic impairment at baseline and hemodynamic deterioration during follow-up. Statin use may be beneficial against hemodynamic deterioration and therefore neuroprotective.

Key Words: carotid artery disease ■ cerebral cortex ■ positron-emission tomography ■ prognosis ■ risk factors

In patients with atherosclerotic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusive disease, the chronic reduction in cerebral perfusion pressure increases the risk of cerebral ischemic damage.1–3 Previous studies have shown that hemodynamic impairment at baseline or hemodynamic deterioration during follow-up is a predictor of subsequent ischemic stroke.2,4,5 Therefore, early detection and careful management of chronic hemodynamic impairment are essential to improve patient prognosis.

In patients with chronic hemodynamic impairment, transient decreases in perfusion pressure can reduce perfusion below the penumbra threshold for a period of minutes, which may cause selective neuronal damage.6–8 Experimental models have demonstrated the development of selective neuronal necrosis after arterial occlusion with resultant ischemia of moderate severity.9–11 However, the pathophysiology of neuronal damage after chronic hemodynamic impairment in humans has not been well studied because of difficulties with in vivo imaging.

Because most cortical neurons express central-type benzodiazepine receptors (BZR), specific imaging of these receptors has made possible the in vivo visualization of neuronal alterations induced by ischemia.10,12,13 Selective neuronal damage can be detected in humans using positron emission tomography (PET) and 11C-flumazenil (FMZ), a neuronal tracer. This mode of imaging has been validated against immunohistochemistry in rodent models of stroke.11

Previous cross-sectional studies have demonstrated selective cortical neuronal damage manifesting as a decrease in BZRs in the normal-appearing cerebral cortex of patients, and this damage has been associated with increased oxygen extraction fraction (OEF) (i.e., misery perfusion) in patients...
with atherosclerotic ICA or MCA occlusive disease. However, in these studies, it was unclear whether hemodynamic impairment was directly associated with selective cortical neuronal damage. In a preliminary work performed by our group, we observed that decreases in BZR were correlated with increases in OEF during follow-up in 17 patients with atherosclerotic ICA or MCA disease. Indeed, hemodynamic deterioration during follow-up may be a risk factor for the progression of cortical neuronal damage. The elucidation of these relationships is clinically important: vascular reconstruction surgery is an option that can improve chronic hemodynamic impairment, and thus research is needed to determine whether surgical intervention should be used to prevent the development of selective neuronal damage in patients with hemodynamic impairment. Additionally, given its association with cognitive impairment, selective neuronal damage may constitute a novel and important target for the treatment of patients with chronic hemodynamic impairment.

The purpose of this longitudinal study was to determine whether selective cortical neuronal damage manifests as a decrease in BZR in the normal-appearing cerebral cortex of patients with atherosclerotic ICA or MCA occlusive disease and furthermore whether these changes can be correlated with chronic hemodynamic impairment at baseline or hemodynamic deterioration.

### Methods

#### Patients

We studied 80 patients, aged 63±8 (mean±SD) years, including 52 men and 28 women, with atherosclerotic occlusion or stenosis of the ICA or MCA using PET (Table 1). Seventeen patients were part of a previously published data set. Patients were referred to our PET unit for evaluation of the hemodynamic effects of ICA or MCA disease as part of a comprehensive clinical evaluation to determine the necessity of vascular reconstruction surgery.

Inclusion criteria were as follows: (1) occlusion or stenosis of the ICA (>60% diameter reduction according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria) or MCA (>50% diameter reduction) as documented by conventional or magnetic resonance angiography, (2) functional independence in daily life (a modified Rankin Scale score <3), (3) for symptomatic patients, history of transient ischemic attack or minor completed stroke in ICA or MCA distribution, (4) medically treated patients with no intervening transient ischemic attack or stroke since the first PET examination, and (5) availability and willingness to return for follow-up PET examination. Transient ischemic attack was defined as focal symptoms of presumed ischemic cerebrovascular origin lasting <24 hours. Exclusion criteria were (1) cerebral–cortical, cerebellar, or brain stem infarct detectable on routine magnetic resonance imaging (MRI) (T2-weighted, T2-weighted, or fluid-attenuated inversion recovery imaging) or computed tomography imaging, (2) history of vascular reconstruction surgery, (3) unilateral arterial disease with extensive white matter lesions in both hemispheres probably caused by bilateral small vessel disease, (4) history of taking BZR agonists, and (5) presence of potential sources of cardiogenic embolism.

Of 80 patients, 25 were asymptomatic, 17 had transient ischemic attack, and 38 had completed stroke. In the same patient cohort, 33 had ICA occlusion, 10 had ICA stenosis, 28 had MCA occlusion, and 9 had MCA stenosis. The interval between the first and follow-up PET studies ranged from 3 to 108 months (mean: 26±20 months). During follow-up, 59 patients were treated with antiplatelet therapy (aspirin, ticlopidine HCl, or clopidogrel) and 27 patients were treated with statin. For 22 patients, statin treatment was combined with antiplatelet agents.

For vascular risk factors, status with respect to hypertension, diabetes mellitus, ischemic heart disease, hypercholesterolemia, and smoking was evaluated from patient history recorded at the first PET examination. Hypertension, diabetes mellitus, ischemic heart disease, or hypercholesterolemia was judged to be present when there was a history of treatment.

To establish a control database for BZR imaging, we studied 10 healthy control subjects, aged 57±7 years, including 7 men and 3 women with no history of medical or psychiatric disorder or of taking BZR agonists. Among them, 7 subjects, aged 56±8 years, including 4 men and 3 women, attended follow-up PET examinations. The interval between the first and follow-up PET studies ranged from 38 to 45 months (mean: 41±3 months). All protocols in this study were approved by the ethics committee of our center, and all subjects gave in written informed consent.

#### PET Measurements

PET scans were performed in each subject using an Advance whole-body scanner (General Electric Medical Systems, Wauwatosa, WI), which permits the simultaneous acquisition of 35 image slices with an interslice spacing of 4.25 mm. After a transmission scan using 68Ge/68Ga, a series of 15O-gas studies was performed. Briefly, C15O2 and 15O2 were delivered continuously to the patient via a mask for the duration of a 5-minute scan. Cerebral blood volume (CBV) was measured by bolus inhalation of C15O with scanning for 3 minutes. Arterial samples were obtained during scanning. No subject showed significant changes in PaCO2 during scanning.

#### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>34.7±32.8*</td>
<td>19.3±26.4</td>
</tr>
<tr>
<td>Follow-up</td>
<td>69.2±59.0*</td>
<td>17.9±24.5</td>
</tr>
</tbody>
</table>

Comparative values for BZR index in 10 control subjects was 1.78±1.79. BZR indicates benzodiazepine receptor; ICA, internal carotid artery; and MCA, middle cerebral artery.

*P<0.05 vs no group.
The 15O-gas study was followed by a study of 11C-FMZ, which was synthesized by 11C-methylation of demethylated-FMZ (Hoffmann-La Roche, Basel, Switzerland). After the slow intravenous injection of 11C-FMZ, a 50-minute dynamic PET scan was initiated.

We used the steady-state method to calculate cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2), and OEF.20 The CMRO2 and OEF were corrected on the basis of CBV. The binding potential (BP [nondisplaceable]) of 11C-FMZ was calculated using dynamic data and Logan graphical analysis with reference tissue, with the pons as the reference region.19,21

Data Analysis

The 15O gas PET-scanning analysis used a classical region-of-interest (ROI) analysis. We analyzed 10 tomographic planes, located 46.25 to 84.5 mm above and parallel to the orbitomeatal line.22 The lowest plane corresponded to the level of the basal ganglia and the thalamus, and the uppermost plane corresponded to the level of the centrum semiovale. A ROI was selected for CBF images. Each image was examined by compactly placing 10 to 12 circular ROIs (diameter: 16 mm) over the gray matter of the outer cortex in each hemisphere. According to the atlas,23 the ROIs in all 10 images covered the distribution of the MCA as well as the external border zone regions.22,23 The same ROIs were used for the CMRO2, OEF, and CBV images. The mean hemispheric value for the hemisphere affected by ICA or MCA disease was calculated as the average of all the circular ROIs.

FMZ BP parametric images were analyzed using a 3D stereotactic surface projection technique, as previously described.7,24 This technique anatomically normalized individual PET data to the standard brain and compared regional voxel data between patients and controls. In the standard stereotactic system, pixels located on the outer and medial surfaces of both hemispheres and vectors perpendicular to the 3D surface at each pixel were predetermined. For each predetermined surface pixel on an individual’s anatomically standardized PET image set, the algorithm searched along the vector, 6 pixels deep into the cortex, for the highest pixel value, and assigned this maximum value to the surface pixel. To correct for fluctuations in whole-brain values and to extract the changes because of ICA or MCA disease, the pixel values of an individual’s image set were normalized to the mean cerebellar value before analysis. Z scores were calculated for each surface pixel (calculated as [mean normalized pixel value for controls − normalized pixel value for the patient]/SD for controls) and used to quantify decreases in FMZ BP. Thus, a positive Z score in a patient represented reduced FMZ BP relative to the control group.

To quantify the degree of abnormal FMZ BP reduction in each patient, the stereotactic extraction estimation method was used to calculate a BZR index (defined as [% pixels with Z score >2] × [average Z score for those pixels]) for the cerebral–cortical MCA distribution affected by ICA or MCA disease.25 This MCA distribution included the middle and inferior frontal gyri; the precentral gyrus; the superior and inferior parietal gyri; the angular, postcentral, and supramarginal gyri; the superior, middle, inferior, and transverse temporal gyri; and the superior and middle occipital gyri.25

At follow-up examinations, total change in the BZR index or the CBF, CMRO2, OEF, CBV, or CBF/CBV values in the MCA distribution with arterial disease was calculated by subtracting the values obtained at the follow-up examination from those obtained at the first examination. In controls, the calculation was performed using the mean of the bilateral hemispheric values of the BZR index. The mean±SD value of changes in the index in the controls was 0.94±1.38. In patients, increase of the
index beyond the upper 95% limit (the mean plus $t_{0.05}$SD) defined in normal subjects (above 4.32) was considered to be an increased BZR index (progression of neuronal damage) during follow-up.

Statistical Analysis

Clinical backgrounds were compared between groups using the Student $t$ test, Mann–Whitney $U$ test, or Fisher exact test, as appropriate. The relationships between variables were analyzed using simple or multiple regression analyses or the Spearman rank correlation analysis, as appropriate. A multivariable logistic regression model with a forward stepwise selection procedure was used to test the independent predictive value of PET hemodynamic variables at baseline and the change in variables during follow-up with respect to the increased BZR index. For all analyses, statistical significance was accepted at $P<0.05$.

Results

Forty patients (50%) showed an increase in BZR index beyond the upper 95% limit defined in normal subjects (Figures 1 and 2). No patient characteristics significantly differed between the 2 groups, except for BZR index (Table 1).

In the hemisphere affected by arterial disease, $T_2$-weighted MRI at the follow-up evaluation disclosed extension of the preexisting confluent white matter lesions in 1 stroke patient and an increase in punctate high-intensity lesions in the subcortical white matter of 1 asymptomatic patient and in the thalamus of 1 stroke patient. In the hemisphere contralateral to arterial disease, an increase in punctate high-intensity lesions in the basal ganglia was identified in 2 stroke patients. The other 75 patients did not show apparent MRI changes at follow-up. The incidence of these changes did not significantly differ between patients with or without an increased BZR index at follow-up (3/40 versus 2/40; Fisher exact test, $P>0.99$).

Follow-up findings on MR angiography included an increase in the degree of stenosis in 1 patient with MCA stenosis and in 3 patients with ICA stenosis and apparent stenosis in 2 patients (severe stenosis of the branch of the ipsilateral MCA and mild stenosis of the contralateral PCA). The incidence of these MR angiography changes significantly differed between patients with and without an increased BZR index at follow-up (6/40 versus 0/40; Fisher exact test, $P=0.025$).

Patients with an increased BZR index in follow-up imaging had a lower CBF value at baseline, lower CBF, CMRO$_2$, and CBF/CBV values at follow-up, and a tendency towards higher OEF values that approached statistical significance at follow-up ($P=0.06$), and a larger change in the OEF at follow-up ($P=0.13$; Table 2). Changes in the OEF at follow-up were negatively correlated with OEF values at baseline in patients with a lower CBF value at baseline, lower CBF, CMRO$_2$, or CBF/CBV at baseline and changes in those values during follow-up, CBF at baseline and change (increase) in the OEF during follow-up emerged as significant independent predictors for increases in the BZR index (Table 3, model 1). The CBF value at baseline and change in the OEF during follow-up were also significant independent predictors of the increase of the BZR index, after inclusion of the interval between the first and follow-up PET examinations in the model (model 2). Changes in the BZR index during follow-up were negatively correlated with CBF values at baseline and positively correlated with changes in the OEF during follow-up (Figure 2).

A multiple linear regression analysis (forward stepwise selection) was used to investigate the contribution of primary ischemia (misery perfusion) and secondary reduction of CBF because of decreased metabolism (selective neuronal damage or deafferentation caused by subcortical ischemic lesions) to CBF value at baseline. Our analysis produced a model that included the OEF value and the BZR index at baseline with a correlation coefficient of 0.687 for the CBF value at baseline ($P<0.01$), in which the OEF and BZR index accounted for 31.5% and 14.3% of the variance in CBF, respectively. The presence of subcortical ischemic lesions did not significantly contribute to the magnitude of the correlation. Furthermore, the OEF value (%) (coefficient, $-0.50$; SE, 0.094; $t=-5.37$; $P<0.01$) and the BZR index (coefficient, $-0.095$; SE, 0.021; $t=-4.65$; $P<0.01$) were negatively correlated with the CBF value.

We also investigated the association of changes in the OEF during follow-up with the presence of vascular risk factors and drug treatment history (shown in Table 1). A multiple linear regression analysis (forward stepwise selection) produced a model that included statin use during follow-up.

Table 2. $^{15}$O-Gas PET Variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Increase in BZR Index During Follow-Up</th>
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<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>CBF, mL/(100 g·min)</td>
<td>32.9±6.7*</td>
</tr>
<tr>
<td>CMRO$_2$, mL/(100 g·min)</td>
<td>2.97±0.41</td>
</tr>
<tr>
<td>OEF, %</td>
<td>50.9±7.5</td>
</tr>
<tr>
<td>CBV, ml/100g</td>
<td>3.42±0.56</td>
</tr>
<tr>
<td>CBF/CBV, min$^{-1}$</td>
<td>9.74±1.93</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>CBF, mL/(100 g·min)</td>
<td>31.9±6.7*</td>
</tr>
<tr>
<td>CMRO$_2$, mL/(100 g·min)</td>
<td>2.94±0.40*</td>
</tr>
<tr>
<td>OEF, %</td>
<td>53.3±6.4</td>
</tr>
<tr>
<td>CBV, ml/100g</td>
<td>3.43±0.58</td>
</tr>
<tr>
<td>CBF/CBV, min$^{-1}$</td>
<td>9.41±1.68*</td>
</tr>
<tr>
<td>CBF change, mL/(100 g·min)</td>
<td>−0.9±6.6</td>
</tr>
<tr>
<td>CMRO$_2$ change, mL/(100 g·min)</td>
<td>−0.02±0.38</td>
</tr>
<tr>
<td>OEF change, %</td>
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</tr>
<tr>
<td>CBV change, ml/100g</td>
<td>0.00±0.47</td>
</tr>
<tr>
<td>CBF/CBV change, min$^{-1}$</td>
<td>−0.33±2.06</td>
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</table>

Normal values for CBF, CMRO$_2$, OEF, CBV, and CBF/CBV in the 7 controls were 44.6±4.5, 3.43±0.33, 44.5±3.8, 3.98±0.48, and 11.4±1.8, respectively. BZR indicates benzodiazepine receptor; CBF, cerebral blood flow; CBV, cerebral blood volume; CMRO$_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; and PET, positron emission tomography.

* $P<0.05$ vs no group.
and the presence of hypercholesterolemia with a correlation coefficient of 0.323 for change in the OEF during follow-up ($P=0.014$), in which statin use and hypercholesterolemia accounted for 3.8% and 4.3% of the variance of the change in the OEF, respectively. Furthermore, statin use (no=0 and yes=1; coefficient, −8.55; SE, 2.88; $t=−2.96$; $P<0.01$) was negatively correlated with the change in the OEF, whereas the presence of hypercholesterolemia (no=0 and yes = 1; coefficient, 5.94; SE, 2.74; $t=2.16$; $P<0.05$) was positively correlated with change in the OEF.

Twenty-five asymptomatic patients were included in this study. Twelve asymptomatic patients had an increased BZR index during follow-up, whereas 13 did not (12/40 versus 13/40; Fisher exact test, $P>0.99$). Asymptomatic patients had a lower BZR index and higher CBF, CMRO$_2$, and CBF/CBV at baseline than symptomatic patients (Table 4). At follow-up, no measures differed between these 2 groups. Changes in the BZR index did not significantly differ between the symptomatic and asymptomatic patients. Changes in CMRO$_2$, CBV, and CBF/CBV values were significantly different between these 2 patient groups.

**Discussion**

This longitudinal study demonstrates an association between chronic hemodynamic impairment and the progression of selective cortical neuronal damage in patients with atherosclerotic ICA or MCA disease and no ischemic episodes of stroke during follow-up. Selective cortical neuronal damage during follow-up was indicated by an increase in the BZR index of the normal-appearing cerebral cortex and was predicted by decreased CBF at baseline and a change (increase) in the OEF during follow-up. Additionally, increases in the OEF during follow-up were most commonly detected in patients who did not use statins.

Hemodynamic impairment at baseline may be a predictor for progressive selective cortical neuronal damage and subsequent ischemic stroke in patients with atherosclerotic ICA or MCA disease. In this study, we found that decreased CBF associated with the progression of cortical neuronal damage was explained by an increased OEF and increased BZR index at baseline, suggesting that the decreased CBF may have been a reflection of both misery perfusion and decreased cortical metabolism. Patients with an increased OEF (misery perfusion) have a marginally adequate blood supply relative to metabolic demand, which increases the risk of cerebral ischemia.$^{1,3}$ Therefore, it is reasonable to hypothesize that misery perfusion at baseline is associated with subsequent development of ischemic cortical neuronal damage. The contribution of the increased BZR index at baseline suggests that patients with misery perfusion have already suffered some ischemic cortical neuronal damage and may be at particular risk for progressive cortical neuronal damage.

Hemodynamic deterioration during follow-up may also increase the risk of subsequent selective cortical neuronal damage, particularly in patients who do not have misery perfusion at baseline.$^3$ In this study, the progression of cortical neuronal damage was also associated with an increased OEF during follow-up, which is indicative of hemodynamic deterioration. The relationship between an increased BZR index and an increased OEF during follow-up became apparent after adjusting for the effects of decreased CBF at baseline. Changes in the OEF during follow-up were negatively correlated with OEF values at baseline, which indicated that patients without misery perfusion at baseline experienced larger increases in the OEF during follow-up. In patients without misery perfusion at baseline, large reductions in perfusion associated with an increased OEF led to subsequent neuronal damage (Figure I in the online-only Data Supplement). Alternatively, among patients with misery perfusion at baseline, small reductions in cerebral

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| Table 3. Multivariable Logistic Regression Analysis With Increased BZR Index in the Hemisphere With Arterial Disease as the Dependent Variable |
|---|---|---|---|
| **Independent Variable** | **Odds Ratio** | **95% Confidence Interval** | **$P$ Value** |
| **Model 1** | | | |
| CBF, mL/(100 g-min) | 0.902 | 0.839–0.970 | 0.0057 |
| OEF change, % | 1.090 | 1.014–1.171 | 0.0195 |
| **Model 2** | | | |
| CBF, mL/(100 g-min) | 0.900 | 0.836–0.970 | 0.0055 |
| OEF change, % | 1.086 | 1.009–1.169 | 0.0195 |
| Interval, mo | 1.017 | 0.991–1.043 | 0.2125 |

BZR indicates benzodiazepine receptor; CBF, cerebral blood flow; and OEF, oxygen extraction fraction.
The precise reason for the hemodynamic deterioration can be unclear in individual patients; however, the aggravation of vascular risk factors and the progression of athero- or arteriosclerosis may lead to chronic decreases in collateral flow. In this study, the progression of arteriosclerosis on MR angiography was associated with an increased BZR index. An increased OEF during follow-up was associated with the presence of hypercholesterolemia and a lack of statin use during follow-up. Appropriate control of vascular risk factors and statin use may therefore have beneficial effects against hemodynamic deterioration and lead to neuronal protection. Indeed, statin use may reduce the occurrence of selective neuronal damage and infarction because of large artery arteriosclerosis. Several studies have shown that statins have beneficial effects on cerebral circulation and brain parenchyma during ischemic stroke and reperfusion.

The impact of progressive cortical neuronal damage on clinical outcomes is unclear in this study. Some patients developed new cortical symptoms, which were associated with regional cortical neuronal damage (Figure I; Figure I in the online-only Data Supplement). However, we could not systematically investigate cognitive differences among these patients. Previous cross-sectional studies have demonstrated selective cortical neuronal damage manifested as a decrease in BZRs, which was associated with subtle cognitive impairment. However, a causal relationship between selective neuronal damage and cognitive impairment should be confirmed using follow-up studies. However, standard clinical stroke scales may not be sensitive to subtle cognitive impairments. Furthermore, systematic neuropsychological tests may be needed to detect variable cortical dysfunction caused by regional differences of progressive neuronal damage.

To address these issues, Chida et al used a neuropsychological battery consisting of the Wechsler Adult Intelligence Scale Revised, the Wechsler Memory Scale, and Rey–Osterreith Complex Figure test, before and after carotid endarterectomy. Cerebral hyperperfusion or ischemia after carotid endarterectomy was found to result in a decrease in BZRs that correlated with postoperative cognitive impairment in the absence of new lesions on MRI. Alternatively, improvement of the hemodynamic compromise after carotid endarterectomy was associated with a postoperative increase in BZRs, which was correlated with improved cognitive performance. Therefore, progressive cortical neuronal damage may contribute to the development of subtle poststroke cognitive impairment dependent on the extent on the damage.

The BZR index increased dramatically between baseline and follow-up, whereas changes in hemodynamic or metabolic parameters were less clear. This was especially true in symptomatic patients (Table 4). In patients with subcortical stroke at baseline, functional recovery with increased CMRO_2 may have occurred during follow-up. This process may be independent of decreased BZRs during follow-up. Furthermore, hemodynamic impairment may improve after neuronal damage because of the slow improvement of collateral blood flow. Therefore, the change in the hemodynamic or metabolic parameters may be more complex than that for the BZR index, which may affect associations between it and hemodynamic or metabolic parameters.

### Table 4. PET Variables for Asymptomatic and Symptomatic Patients

<table>
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<tr>
<th>Characteristic</th>
<th>Asymptomatic (25)</th>
<th>Symptomatic (55)</th>
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<tr>
<td>BZR index</td>
<td>16.2±13.5*</td>
<td>31.8±34.9</td>
</tr>
<tr>
<td>CBF, mL/(100 g·min)</td>
<td>37.9±5.7*</td>
<td>33.2±7.5</td>
</tr>
<tr>
<td>CMRO_2, mL/(100 g·min)</td>
<td>3.29±0.39*</td>
<td>2.95±0.38</td>
</tr>
<tr>
<td>OEF, %</td>
<td>50.5±6.8</td>
<td>50.9±6.7</td>
</tr>
<tr>
<td>CBV, ml/100g</td>
<td>3.50±0.61</td>
<td>3.50±0.59</td>
</tr>
<tr>
<td>CBF/CBV, min⁻¹</td>
<td>11.13±2.29*</td>
<td>9.58±1.97</td>
</tr>
<tr>
<td>Follow-up</td>
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<tr>
<td>BZR index</td>
<td>29.2±31.0</td>
<td>50.1±57.9</td>
</tr>
<tr>
<td>CBF, mL/(100 g·min)</td>
<td>36.2±5.9</td>
<td>32.9±7.5</td>
</tr>
<tr>
<td>CMRO_2, mL/(100 g·min)</td>
<td>3.14±0.33</td>
<td>2.99±0.43</td>
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<tr>
<td>OEF, %</td>
<td>51.0±7.3</td>
<td>52.4±5.8</td>
</tr>
<tr>
<td>CBV, ml/100g</td>
<td>3.61±0.56</td>
<td>3.41±0.58</td>
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<tr>
<td>CBF/CBV, min⁻¹</td>
<td>10.16±1.94</td>
<td>9.72±1.98</td>
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<tr>
<td>BZR index change, %</td>
<td>12.6±23.6</td>
<td>18.4±39.0</td>
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<tr>
<td>CBF change, mL/(100 g·min)</td>
<td>−1.7±5.1</td>
<td>−0.3±6.7</td>
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<tr>
<td>CMRO_2 change, mL/(100 g·min)</td>
<td>−0.15±0.35*</td>
<td>0.38±0.36</td>
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<tr>
<td>OEF change, %</td>
<td>0.56±7.04</td>
<td>1.45±7.70</td>
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<tr>
<td>CBV change, ml/100g</td>
<td>0.11±0.31*</td>
<td>−0.08±0.447</td>
</tr>
<tr>
<td>CBF/CBV change, min⁻¹</td>
<td>−0.96±1.72*</td>
<td>0.14±1.85</td>
</tr>
</tbody>
</table>

BZR indicates benzo diazepine receptor; CBF, cerebral blood flow; CBV, cerebral blood volume; CMRO_2, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; and PET, positron emission tomography. *P<0.05 vs symptomatic group.

perfusion and small increases in the OEF were sufficient to produce neuronal damage. The development of this damage may have, in turn, decreased the OEF by decreasing the metabolic demand of the tissue (Figure 1). Furthermore, OEF may decline after neuronal damage because of slow improvement of collateral blood flow. These hypotheses explain why adjusting for decreased CBF at baseline uncovered the association between increased BZR index and an increased OEF during follow-up. Indeed, the contribution of hemodynamic deterioration to selective neuronal damage during follow-up differed between patients with and without misery perfusion at baseline.

The findings presented here have important implications for the clinical prevention of cortical neuronal damage by atherosclerotic ICA or MCA disease. First, it should be recognized that the progression of selective cortical neuronal damage occurs in association with chronic hemodynamic impairment and in the absence of an overt stroke episode. Thus, evaluation of hemodynamic status at baseline or follow-up is essential for the prevention of subsequent neuronal damage. Vascular reconstruction surgery can improve hemodynamic impairment and therefore may be indicated for patients vulnerable to selective neuronal damage.

The precise reason for the hemodynamic deterioration can be unclear in individual patients; however, the aggravation of vascular risk factors and the progression of athero- or arteriosclerosis may lead to chronic decreases in collateral flow. In this study, the progression of arteriosclerosis on MR angiography was associated with an increased BZR index. An increased OEF during follow-up was associated with the presence of hypercholesterolemia and a lack of statin use during follow-up. Appropriate control of vascular risk factors and statin use may therefore have beneficial effects against hemodynamic deterioration and lead to neuronal protection. Indeed, statin use may reduce the occurrence of selective neuronal damage and infarction because of large artery arteriosclerosis. Several studies have shown that statins have beneficial effects on cerebral circulation and brain parenchyma during ischemic stroke and reperfusion.

The impact of progressive cortical neuronal damage on clinical outcomes is unclear in this study. Some patients developed new cortical symptoms, which were associated with regional cortical neuronal damage (Figure 1; Figure I in the online-only Data Supplement). However, we could not systematically investigate cognitive differences among these patients. Previous cross-sectional studies have demonstrated selective cortical neuronal damage manifested as a decrease in BZRs, which was associated with subtle cognitive impairment. However, a causal relationship between selective neuronal damage and cognitive impairment should be confirmed using follow-up studies. However, standard clinical stroke scales may not be sensitive to subtle cognitive impairments. Furthermore, systematic neuropsychological tests may be needed to detect variable cortical dysfunction caused by regional differences of progressive neuronal damage.

The findings presented here have important implications for the clinical prevention of cortical neuronal damage by atherosclerotic ICA or MCA disease. First, it should be recognized that the progression of selective cortical neuronal damage occurs in association with chronic hemodynamic impairment and in the absence of an overt stroke episode. Thus, evaluation of hemodynamic status at baseline or follow-up is essential for the prevention of subsequent neuronal damage. Vascular reconstruction surgery can improve hemodynamic impairment and therefore may be indicated for patients vulnerable to selective neuronal damage.
Our previous cross-sectional study did not support a relationship between the extent of subcortical ischemic lesioning and the BZR index, which failed to support the hypothesis that deafferentation because of subcortical infarct caused the decrease in BZR. In this study, progression of subcortical ischemic changes was not correlated with an increased BZR index. This suggests that the effect of subcortical ischemic lesions on cortical neuronal damage may not be large.

Limitations
This study had some limitations. Different sampling methods were used for the BZR and hemodynamic parameters. FMZ BP parametric images were analyzed using a 3D stereotactic surface projection technique, which was based on a pixel-to-pixel analysis. The BZR index was defined as (% pixels with Z score >2) x (average Z score for those pixels). Thus, this index can reflect both the extent and the severity of decreased BZR. Small foci of BZR decreases can be detected sensitively and are indicated by an increase in the BZR index. The method for 15O gas PET-scanning analysis used a classical ROI analysis. Calculation of the mean hemispheric value using ROIs placed compactly on multiple image slices could help to diminish error in the definition of an ROI. However, regional changes of the PET measures may be overlooked using these methods. These differences may contribute to the discrepancy between increased BZR and changes in hemodynamic and metabolic parameters. Our study was unable to correct for partial volume effects using MRI because imaging was only performed for clinical purposes. A decrease in cortical FMZ binding could at least partly reflect an increase in cortical atrophy because of ischemic tissue damage (ie, neuronal loss and partial volume effects) as well as decreases in tissue BZR expression. The normal control database was based on scans from only 10 healthy control subjects who were significantly younger than our patients. Additionally, follow-up examinations demonstrating no significant change in Z index during follow-up (mean: 41±3 months) were performed on only 7 of these 10 control subjects.

Conclusions
In patients with atherosclerotic ICA or MCA disease, the progression of selective cortical neuronal damage occurs in the absence of an overt stroke episode and in association with hemodynamic impairment and an appropriate control of vascular risk factors (eg, the use of statin) may be useful.

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Disclosures
None.

References


Progressive Cortical Neuronal Damage and Chronic Hemodynamic Impairment in Atherosclerotic Major Cerebral Artery Disease
Hiroshi Yamauchi, Shinya Kagawa, Yoshihiko Kishibe, Masaaki Takahashi and Tatsuya Higashi

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ONLINE SUPPLEMENT

Title: Progressive cortical neuronal damage and chronic hemodynamic impairment in atherosclerotic major cerebral artery disease

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Example of a decrease of benzodiazepine receptor (BZR) with hemodynamic deterioration in a 70-year-old man with right middle cerebral artery (MCA) occlusion (Figure 4 in ref. 1).

The first PET study (first row) shows a mild decrease of flumazenil-binding potential (FMZ-BP), cerebral blood flow (CBF), and cerebral metabolic rate of oxygen (CMRO₂) with a slight increase of oxygen extraction fraction (OEF) in the right (R) hemisphere with MCA occlusion and subcortical infarction (MRI). The follow-up study 15 months later (second row) shows a decrease of FMZ-BP, CBF, and CMRO₂ with increased OEF in the right hemisphere. The mean hemispheric value of CBF decreased from 26.4 to 22.0 (ml/100g/min) and the OEF value increased from 50.8 to 59.2 (%). 3D-SSP images and Z score maps at the first (third row) and second (fourth row) examinations show a decrease of FMZ-BP in the right hemisphere. The extent of abnormally decreased BZR increased from 6.4% to 22.6% in the right MCA distribution, the mean z scores in those pixels from 2.73 to 2.74, and the abnormally decreased BZR index from 17.6 to 61.9. The patient had constructive disturbance due to possible parietal lobe dysfunction (Kohs test; IQ <60).

Reference
动脉粥样硬化性脑大动脉病变的进行性皮层神经元损伤及慢性血流动力学障碍关系的研究

Progressive Cortical Neuronal Damage and Chronic Hemodynamic Impairment in Atherosclerotic Major Cerebral Artery Disease

Hiroshi Yamauchi, MD, PhD; Shinya Kagawa, MS; Yoshihiko Kishibe, RT; Masaaki Takahashi, RT; Tatsuya Higashi, MD, PhD

背景及目的: 许多横断面研究表明慢性血流动力学损害可能在动脉粥样硬化性颈内动脉闭塞或大脑中动脉闭塞患者中导致选择性皮层神经元损伤。本纵向研究的目的是明确皮层神经元损伤的进展通过中枢苯二氮卓受体(benzodiazepine receptors, BZRs)数量下降评价是否与基线血流动力学损害以及随访过程中血流动力学恶化相关。

方法: 本研究 2 次采用11C-氟马西尼-正电子发射断层扫描显像来评价 80 例经治疗且随访期间无脑缺血发作的动脉粥样硬化性颈内动脉或大脑中动脉闭塞患者的 BZRs 分布。采用3维立体定向表面投影技术,通过15O 气体-正电子发射断层扫描监测获得的血流动力学参数的平均半球值,定量研究大脑中动脉分布的皮层区域 BZRs 的异常降低以及 BZR 指数的相关变化。

结果: 在动脉疾病影响的大脑半球,随访期间(平均 26 ± 20 个月)40 例患者(50％)的 BZR 指数上升。多元 Logistic 回归分析结果显示 BZR 指数升高与基线脑血流量下降以及随访期间氧摄取指数升高有关。而随访期间氧摄取指数升高与未使用他汀类药物相关。

结论: 在动脉粥样硬化性颈内动脉病变或大脑中动脉病变患者中,皮层神经元损伤的进展与基线血流动力学破坏以及随访期间血流动力学水平恶化相关。他汀类药物的使用可能有益于阻止血流动力学恶化从而产生神经保护作用。

关键词: 颈动脉疾病; 大脑皮层; 正电子发射断层扫描; 预后; 危险因素

(Stroke. 2016;47:1534-1541. 浙江大学医学院附属第二医院神经内科 陈琳 陈逸 译 楼敏 校)

动脉粥样硬化性颈内动脉闭塞或大脑中动脉闭塞的慢性大脑灌注压降低导致脑缺血损伤风险增加1-3。既往研究表明基线血流动力学障碍或随访中血流动力学恶化是继发缺血性卒中的预测因素2,4,5。因此,早期发现并有效干预慢性血流动力学破坏对于改善患者预后是至关重要的。

在慢性血流动力学破坏的患者中,短暂的脑灌注压降低可导致一段时间内的灌注低于半暗带阈值,从而选择性损伤部分神经元6-8。实验模型中证明了动脉闭塞及中度缺血后存在选择性神经元坏死进展9-11。但是,由于活体成像的困难,在人身上慢性血流动力学障碍后神经元损伤的病理生理学过程还没有得到充分的研究。

由于大多数皮层神经元都表达中枢型苯二氮卓受体(benzodiazepine receptors, BZRs),因此对这些受体特异性成像可以实现活体内可视化观察缺血诱导的神经元变化10,12,13。人体内选择性神经元损伤可以采用正电子发射断层扫描(positron emission tomography, PET)和神经示踪剂11C-氟马西尼(flumazenil, FMZ)来监测。这种成像模型已在啮齿类动物的卒中模型中经由免疫组化验证11。

既往的横断面研究表明选择性皮层神经元损伤表现为患者大脑皮层处 BZRs 下降,虽然外观形态尚不受影响,且这种损伤与动脉粥样硬化性 ICA 或 MCA 闭塞患者氧摄取指数(oxygen extraction fraction, OEF)增加(例如,贫困灌注1)有关7,8。但是,这些研究未表明血流动力学障碍是否与选择性皮层神经元损伤直接相关。本研究在前期工作中观察到17例动脉粥样硬化性 ICA 闭塞或 MVA 闭塞患者在随访中 BZRs 下降与 OEF 增加相关7。事实上,随访中血流动力学恶化可能是皮层神经元损伤进展的危险因素。阐明这些关系在临床上有重要意义:血管重建术是改善慢性血流动力学障碍的一种方法1,因此需要研究来确定是否应该采用外科手术干预以防止血流动力学障碍的患者选择性神经元损伤的进展。此外,由于选择性神经元损伤与认知障碍相关,因此前者也可能为慢性血流动力学障碍患者的治疗提供一个新的重要靶点14,15。

本纵向研究旨在明确选择性皮层神经元损伤是否表现为动脉粥样硬化性 ICA 闭塞或 MVA 闭塞患者正常外观大脑皮层处的 BZRs 下降,并进一步明确这些改变是否与慢性血流动力学障碍或血流动力学恶化相关。

方法

患者

研究对象是 80 例经过 PET 检查的动脉粥样硬化性 ICA 或 MCA 闭塞或狭窄的患者,年龄 63 ± 8 年(标准差, SD)岁,其中包括 52 例男性及 28 例女性(表 1)。其中 17 例患者的资料为既往发表数据的一部分7。通过 PET 评价患者 ICA
或 MCA 病变血流动力学的影响以作为临床综合评价的一部分，从而确定是否需要进行血管重建术。

纳入标准：(1) 通过常规检查或磁共振血管成像，发现 ICA 狭窄或闭塞 [ 根据北美症状性颈动脉内膜切除试验 (North American Symptomatic Carotid Endarterectomy Trial, NASCET) 标准，血管内径减少 >60%] 或 MCA 狭窄 (血管内径减少 >50%); (2) 日常生活功能独立 (改良 Rankin 量表评分 <3); (3) 对于症状性患者，在 ICA 或 MCA 分布区有短暂性脑缺血发作或小卒中史；(4) 药物治疗的患者，在第一次 PET 检查后没有再发生卒中或短暂性脑缺血发作；(5) 可以并愿意做随访 PET 检查。短暂性脑缺血发作定义为由脑动脉缺血所致的局灶神经功能缺损症状持续 <24 h。排除标准：(1) 由常规磁共振成像 (magnetic resonance imaging, MRI) (T1 加权, T2 加权, 或液体衰减反转恢复成像) 或计算机断层扫描 (computed tomography, CT) 成像可检测到的大脑-皮层、小脑、脑干梗死; (2) 既往血管重建手术史; (3) 单侧动脉疾病伴随可能由双侧小血管病引起的双侧半球广泛性白质病变; (4) 有服用 BZR 拮抗剂史的; (5) 存在心源性病因潜在来源。

在这 80 例患者中，有 25 例无症状，17 例有短暂性脑缺血发作，以及 38 例卒中患者。在这些患者中，有 33 例患有 ICA 闭塞，10 例患有 CIA 狭窄，28 例 MCA 闭塞，9 例 MCA 狭窄。第一次 PET 和随访 PET 的时间间隔从 3~108 个月 (评价 26±20 个月)。在随访期间，59 例患者进行了抗血小板治疗 (阿司匹林、盐酸噻氯匹定、氯吡格雷)，27 例患者使用他汀类药物。其中 22 例患者同时使用抗血小板药物和他汀类药物。

第一次 PET 检查时根据患者病史资料评价血管危险因素：高血压、糖尿病、缺血性心脏病、高胆固醇血症和吸烟史等。上述疾病状态如有治疗史即认为存在。

将 10 例无疾病治疗史，无精神疾病且不曾服用 BZR 激动剂的健康对照者用作 BZR 成像的对照，年龄为 57±7 岁，其中包括 7 名男性和 3 名女性。其中 7 例，年龄 56±8 岁，包括 4 名男性和 3 名女性参与了随访 PET 检查。第一次 PET 和随访 PET 时间间隔为从 38~45 个月 (平均 41±3 个月)。本研究所经我中心的伦理委员会批准，所有的受试者均已签署书面知情同意。

PET 评价

图 1 基线左侧颈内动脉闭塞且“贫困灌注”患者 BZR 指数的下降。PET 结果 (第一行) 显示，在左侧颈内动脉闭塞且皮层下出血病变 MRI 的左侧 (L) 半球，FMZ BP 略低，CBF 降低而 OEF 增加 (图 1A)。随访 23 个月后 (第二行) 左侧大脑半球 FMZ-BP，CMRO2 和 OEF 相对降低而 CBF 增加。左侧大脑半球平均 CBF 从 30.1 增加到 35.4 (ml/100g/min)，CMRO2 从 3.45 降至 3.33 (ml/100g/min)，OEF 从 55.4 降至 48.0 (%)。在随访过程中，BZR 指数从基线的 16.0 上升至随访时 52.8。在左侧额叶皮层 BZR 指数上升显著同时其基线 OEF 相对较高。由于额叶功能障碍的患者变得更好斗和易怒。
数据分析

O 气体 PET 扫描分析采用的是经典的感兴趣区(region-of-interest, ROI)分析。分析选取了位于眶听线上方 46.25~84.5 mm 且平行于眶听线的 10 个断层面。最低的平面位于基底节和丘脑水平, 最高的平面位于半卵圆中心水平。选择一个兴趣区用于 CBF 图像。每个图像都是由 10~12 个紧密分布于大脑半球外侧皮质灰质的圆形 ROI(直径 16 mm)检测的。根据图集, 10 个图像的 ROI 都覆盖了 MCA 的分布区及外部边界区域。CMRO2、OEF 和 CBF 图像都使用相同的 ROI。计算所有圆形 ROI 区域内的平均值作为 ICA 或 MCA 疾病影响的大脑半球的半球平均值。

采用前述提到的 3 维立体表面投影技术分析 FMZ BP 参数图像。该技术从解剖上标准化的 PET 图像集中, 对于每个预先确定的表面像素, 该算法会沿着垂直方向深入皮质 6 个像素, 搜索最高像素值, 并将这个最大值作为该表面像素的最高值。为了修正全脑的波动并提取 ICA 或 MCA 导致病变的变化, 个体图像的像素值在分析中标准化为平均全脑值。对每个表面像素计算 Z 分值 (对照组标准化的平均像素值 / 患者标准化的平均像素值) / 对照组的 SD, 并用于决定 FMZ BP 的降低量。因此患者 Z 分值大于正常代表 FMZ BP 相比于对照组降低。

为了定名是否患者异常 FMZ BP 的降低程度, 使用立体定向提取估计方法计算 ICA 或 MCA 病变影响的额叶皮层的 MCA 分布区的 BZR 指数定义为 (Z 分值 >2 的像素 %) × (这些像素的平均 Z 分值)。MCA 分布区包括额中、下回、中央前回、上、下顶回、角、中央后、缘上回; 额上、中、下、横回; 枕上、下回。BZR 指数增加被认为是随访 BZR 指数增加 (神经元损伤进展)。

统计分析

临床数据选择 t-检验、Mann-Whitney U 检验或 Fisher 精确检验进行比较, 变量间关系采用一元或多元回归分析或 Spearman 秩回归分析。多元 logistic 回归模型 - 正向逐步选择程序用于检测 PET 血流动力学变量在基线和随访中关于 BZR 指数增加的变化的独立预测价值。对于所有分析, 接受统计学显著性差异为 P<0.05。

结果

40 例患者 BZR 指数超过正常人 95% 的上限 (图 1,2)。除了 BZR 指数之外, 2 组之间患者其他特征差异无显著性 (表 1)。

随访评价时, 加权 MRI 结果显示, 在动脉病变患侧半球, 1 例中患者原先存在的融合白质病变出现进展, 并且 1 例血肿患者的皮质下白质病变处和 1 例卒中患者的皮质异常点状高信号病变增加。在动脉病变对侧半球, 2 例中患者基底节区点状高信号病变增加。其他 75 例患者 MRI 没有明显变化。这些变化的发生率在随访 BZR 指数增加或不增加的患者人群中差异无显著性 (分别为 3/40 与 24/40; Fisher 精确检验, P=0.99)。

随访的 MR 血管造影结果表明 1 例 MCA 狭窄患者和 3 例 ICA 狭窄患者动脉狭窄程度增加, 其中 2 例患者为明显增加 (同侧 MCA 分支重度狭窄及对侧 PCA 轻度狭窄)。这些 MR 血管造影结果显示狭窄程度变化的发生率在随访 BZR 指数增加或不增加的患者人群中差异显著性 (分别为 6/40 与 0; Fisher 精确检验, P=0.025)。

随访 BZR 指数增加的患者的基线 CBF 值以及随访 ICA、CMRO2、OEF, CBF/CBV 值的总变化量是将随访检查中的值减去第一次检查的值。在对照组中, BZR 指数的计算采用的是双侧半球的平均值。对照组指数增加的变化的平均值为 0.94±1.38。在患者中, 指数增加量超过正常人 95% 的上限 (平均值 +2SD) 的被认为是随访 BZR 指数增加 (神经元损伤进展)。

采用多元 logistic 回归分析 (逐步向前) 分析基线 CBF、CMRO2、OEF 和 CBF/CBV 值以及在随访中关于 BZR 指数增加的变化的独立预测价值。对于所有分析, 接受统计学显著性差异为 P<0.05。
采用多元线性回归分析（逐步向前）考察原发性缺血（贫困灌注）和代谢降低（皮层下缺血性病变导致选择性神经元损伤或传入神经阻滞）导致的 CBF 二次降低对基线 CBF 值的贡献。基线 OEF 值和 BZR 指数与基线 CBF 值的相关系数分别为 0.687（P<0.01），其中 OEF 值和 BZR 指数的贡献分别为 31.5% 和 14.3%。皮层下缺血病变对相关的幅度无显著性贡献。此外，OEF 值 (%)(相关系数 =-0.50; SE =0.094; t =-5.37; P<0.01) 和 BZR 指数(相关系数 =-0.095; SE =0.021; t =-4.65; P<0.01) 与 CBF 值呈负相关。

本研究还探讨了血管危险因素与药物治疗与随访 OEF 变化的关系（表 1）。基于多元线性回归分析法（逐步向前）构建了一个模型并纳入了随访中他汀类药物的使用和高胆固醇血症 2 个因素，它们与随访 OEF 变化量相关系数为 0.323（P=0.014），其中他汀类药物的使用和高胆固醇血症的贡献分别为 3.8% 和 4.3%。此外，他汀类药物的使用与 OEF 变化量呈负相关（不使用 =0, 使用 =1; 相关系数 =-8.55; SE=2.88;t =-2.96; P<0.01)，而高胆固醇血症的存在与 OEF 变化量呈正相关（无 =0、是 =1;相关系数 =5.94; SE =2.74; t =2.16; P<0.05）。

本研究共纳入了 25 例无症状患者。其中 12 例患者随访 BZR 增加, 13 例不增加(12/40 vs 13/40; Fisher 精确检验,P>0.99)。相比于有症状患者, 无症状患者有较高的 BZR 指数和较高的基线 CBF、CMRO2 和 CBF/CBV 值（表 4）。随访中 BZR 增加的患者与基线相比, OEF 增加 (贫困灌注) 的患者血流供应超过代谢需求，这可能会增加脑缺血风险 1,3,5。因此本研究有理由猜想基线贫困灌注与后续缺血性皮层神经元损伤进展相关。基线 BZR 指数增加提示贫困灌注的患者已有损伤并有损伤进展的风险。随访期间血流动力学恶化也可能会增加后续选择性皮层神经元损伤风险, 尤其是那些已有基线贫困灌注的患者 4。本研究发现皮层神经元损伤进展与随访 OEF 增加有关，尤其是那些已有基线贫困灌注的患者 4。本研究发现皮层神经元损伤进展与随访 OEF 增加有关，尤其是那些已有基线贫困灌注的患者 4。本研究发现皮层神经元损伤进展与随访 OEF 增加有关，尤其是那些已有基线贫困灌注的患者 4。本研究发现皮层神经元损伤进展与随访 OEF 增加有关，尤其是那些已有基线贫困灌注的患者 4。本研究发现皮层神经元损伤进展与随访 OEF 增加有关，尤其是那些已有基线贫困灌注的患者 4。本研究发现皮层神经元损伤进展与随访 OEF 增加有关，尤其是那些已有基线贫困灌注的患者 4。
理学测试来检测由进行性神经元损伤的受累区域差异导致不同皮层功能障碍。

为了了解这些问题，Chida 等 14,29 采用由韦氏成人智力量表修订版、韦氏记忆量表、Rey-Osterreith 复杂图形测验等组成的神经心理学指标，对颈动脉内膜切除术前后的患者进行检测。颈动脉内膜切除术后 BZR 指数下降，这与基线 MRI 所测到的术后认知功能障碍相关。因此，皮层神经元损伤进展可能导致无症状中轻微的认知功能障碍，这取决于损伤的程度。

从基线到随访，BZR 指数显著增加，而血流动力学和代谢参数的变化还不清楚。这在症状性患者身上尤其明显。对于基线存在皮层下梗死的患者，可能在随访中会出现认知功能改善并伴随 CMRO2 增加。这过程不依赖于颈内动脉粥样硬化性 ICA 或 MCA 病变患者，选择性皮层神经元损伤进展在无卒中事件发生时出现并且与基线 CBF 下降和随访 OEF 升高相关。基线 CBF 下降可能反映了慢性高血压与皮层神经元损伤，而随访 OEF 增加可能反映了血流动力学恶化。因此，为了防止选择性皮层神经元损伤进展，采用血管重建术改善血流动力学和适当控制血管危险因素 (如，使用他汀类药物) 是很有用的。

局限

本研究具有一定的局限性。对于 BZR 和血流动力学参数的测量采用了不同的抽样方式。FMZ BP 参数图像分析采用的是 3 维立体表面投影技术，这是基于像素到像素的分析。BZR 指数定义为 (Z 得分 >2 的像素百分比) × (这些像素的平均 Z 得分)。因此，这个指数既可以反映 BZR 下降的程度也可以反映严重程度。微小区域的 BZR 降低可以通过 BZR 指数灵敏地被检测到并显示为指数增加。PET 扫描分析检测 15O 气体用的是经典的 ROI 分析。通过多个图层密集排列的感兴趣区来计算平均半球值可以帮助消除 ROI 定义时的误差。然而，使用这种分析方法，PET 测量的区域差异可能会被忽略。这种分析方法的差异可能会导致 BZR 增加与血流动力学和代谢参数变化之间矛盾。本研究不能纠正 MRI 上部分体积效应的影响，因为成像只用于临床。本研究不能纠正 MRI 上部分体积效应的影响，因为成像只用于临床。PET 测量的区域性差异可能会被忽略。这种分析方法的差异可能会导致 BZR 增加与血流动力学和代谢参数变化之间矛盾。本研究不能纠正 MRI 上部分体积效应的影响，因为成像只用于临床。

参考文献

アテローム硬化性脳主幹動脈疾患における進行性皮質神経損傷と慢性血行力学的障害

Progressive Cortical Neuronal Damage and Chronic Hemodynamic Impairment in Atherosclerotic Major Cerebral Artery Disease

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