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

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 (BZRs), is associated with hemodynamic impairment at baseline or hemodynamic deterioration during follow-up.

Methods—We evaluated the distribution of BZRs twice using positron emission tomography and $^{11}$C-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 $^{18}$O 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.

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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. Previous studies have shown that hemodynamic impairment at baseline or hemodynamic deterioration during follow-up is a predictor of subsequent ischemic stroke. 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. Experimental models have demonstrated the development of selective neuronal necrosis after arterial occlusion with resultant ischemia of moderate severity. However, the pathophiology 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 (BZRs), specific imaging of these receptors has made possible the in vivo visualization of neuronal alterations induced by ischemia. Selective neuronal damage can be detected in humans using positron emission tomography (PET) and $^{11}$C-flumazenil (FMZ), a neuronal tracer. This mode of imaging has been validated against immunohistochemistry in rodent models of stroke.

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) (ie, misery perfusion) in patients...
with atherosclerotic ICA or MCA occlusive disease.\textsuperscript{7,8} 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 BZRs were correlated with increases in OEF during follow-up in 17 patients with atherosclerotic ICA or MCA disease.\textsuperscript{7} 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,\textsuperscript{1,9} 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.\textsuperscript{14,15}

The purpose of this longitudinal study was to determine whether selective cortical neuronal damage manifests as a decrease in BZRs 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.\textsuperscript{7} 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\textsuperscript{9} or MCA (>50% diameter reduction\textsuperscript{3}) 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) (T1-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±6 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.\textsuperscript{11} After a transmission scan using $^{99m}$ Tc sestamibi, a series of $^{18}$ O-gas studies was performed.\textsuperscript{10} Briefly, C$^{15}$ O$^{2-}$ and $^{18}$ O$_{2}$ 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 injection of $^{14}$ C$^{15}$ O with scanning for 3 minutes. Arterial samples were obtained during scanning. No subject showed significant changes in PaCO$_{2}$ during scanning.

![Table 1. Patient Characteristics](https://www.ahajournals.org/doi/10.1161/CIR.0000000000000000)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Increase in BZR Index During Follow-Up</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>Yes</td>
</tr>
<tr>
<td>Interval, mean±SD, mo</td>
<td>29±23</td>
</tr>
<tr>
<td>Age, y</td>
<td>64±7</td>
</tr>
<tr>
<td>Sex, men, n</td>
<td>30</td>
</tr>
<tr>
<td>Symptomatic, n</td>
<td>28</td>
</tr>
<tr>
<td>Cerebral ischemic lesion, n</td>
<td>32</td>
</tr>
<tr>
<td>Qualifying artery, n</td>
<td>ICA (occlusion/stenosis) 19 (13/6) 24 (20/4)</td>
</tr>
<tr>
<td>Other medical illness, n</td>
<td>Hypertension 24</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>11</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18</td>
</tr>
<tr>
<td>Smoking habit (current and former), n</td>
<td>13</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>30</td>
</tr>
<tr>
<td>Statins</td>
<td>15</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,15,19 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.12,24 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

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Representative images of decreased benzodiazepine receptor (BZR) in a patient with left internal carotid artery occlusion and misery perfusion at baseline. The first positron emission tomography study (first row) showed a mild decrease in flumazenil-binding potential (FMZ BP) in the left (L) hemisphere with subcortical ischemic lesions (magnetic resonance imaging [MRI]), whereas cerebral blood flow (CBF) was decreased and the oxygen extraction fraction (OEF) was increased (misery perfusion). Follow-up 23 mo later (second row) showed relative decreases in FMZ-BP, cerebral metabolic rate of oxygen (CMRO2), and OEF with increased CBF in the L hemisphere. Mean hemispheric CBF increased from 30.1 to 35.4 (mL/100g per min), CMRO2 decreased from 3.45 to 3.33 (mL/100g per min), and OEF decreased from 55.4 to 48.0 (%). 3D-stereotactic surface projection technique images and Z-score maps from the first (third row) and second (fourth row) examinations demonstrated a decrease in FMZ-BP in the left hemisphere, especially in the frontal lobe. The BZR index increased from 16.0 to 52.8 between baseline and follow-up. An increased BZR index was apparent in the left frontal cortex that showed relatively high OEF at baseline. The patient became more aggressive and irritable, possibly because of frontal lobe dysfunction.
index beyond the upper 95% limit (the mean plus \( \Delta \times SD \)) 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, T2-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, CMRO2, 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 (\( P<0.01 \)), 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. 15O-Gas PET Variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Increase in BZR Index During Follow-Up</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>CBF, mL/(100 g min)</td>
<td>32.9±6.7* 36.4±7.5</td>
</tr>
<tr>
<td>CBF change, mL/(100 g min)</td>
<td>−0.9±6.5 −0.6±5.9</td>
</tr>
<tr>
<td>OEF, %</td>
<td>50.9±7.5 50.7±5.9</td>
</tr>
<tr>
<td>OEF change, %</td>
<td>−0.02±0.38 −0.01±0.36</td>
</tr>
<tr>
<td>CBV, mL/100g</td>
<td>3.42±0.56 3.58±0.62</td>
</tr>
<tr>
<td>CBV change, mL/100g</td>
<td>0.003±0.47 0.053±0.34</td>
</tr>
<tr>
<td>CBF/CBV, min−1</td>
<td>9.74±1.93 10.39±2.39</td>
</tr>
<tr>
<td>CBF/CBV change, min−1</td>
<td>−0.33±2.06 −0.07±1.69</td>
</tr>
</tbody>
</table>

Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Increase in BZR Index During Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, mL/(100 g min)</td>
<td>31.9±6.7* 35.8±7.2</td>
</tr>
<tr>
<td>CBF change, mL/(100 g min)</td>
<td>−0.9±6.6 −0.6±5.9</td>
</tr>
<tr>
<td>OEF, %</td>
<td>53.3±6.4 50.6±5.9</td>
</tr>
<tr>
<td>OEF change, %</td>
<td>2.42±8.66 −0.07±5.90</td>
</tr>
<tr>
<td>CBV change, mL/100g</td>
<td>0.003±0.47 −0.053±0.34</td>
</tr>
<tr>
<td>CBV/CBV change, min−1</td>
<td>−0.33±2.06 −0.07±1.69</td>
</tr>
</tbody>
</table>

Normal values for CBF, CMRO2, OEF, CBV, and CBF/CBV in the 7 controls were 44.6±4.5, 3.4±3.3, 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; CMRO2, 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.$^4$ 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

**Table 3. Multivariable Logistic Regression Analysis With Increased BZR Index in the Hemisphere With Arterial Disease as the Dependent Variable**

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF, mL/(100 g·min)</td>
<td>0.902</td>
<td>0.839–0.970</td>
<td>0.0057</td>
</tr>
<tr>
<td>OEF change, %</td>
<td>1.090</td>
<td>1.014–1.171</td>
<td>0.0195</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF, mL/(100 g·min)</td>
<td>0.900</td>
<td>0.836–0.970</td>
<td>0.0055</td>
</tr>
<tr>
<td>OEF change, %</td>
<td>1.086</td>
<td>1.009–1.169</td>
<td>0.0195</td>
</tr>
<tr>
<td>Interval, mo</td>
<td>1.017</td>
<td>0.991–1.043</td>
<td>0.2125</td>
</tr>
</tbody>
</table>

BZR indicates benzodiazepine receptor; CBF, cerebral blood flow; and OEF, oxygen extraction fraction.
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 atherosclerotic lesions may lead to chronic decreases in collateral flow. In this study, the progression of atherosclerosis 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 atherosclerosis. 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.

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.
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) × (average Z score for those pixels). This, thus, the 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 $^{15}$O 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 both decreased CBF at baseline and an increased OEF during follow-up. Decreased CBF at baseline may reflect misery perfusion with cortical neuronal damage, whereas an increased OEF during follow-up may reflect hemodynamic deterioration. Thus, to prevent the progression of selective cortical neuronal damage, vascular reconstruction surgery to improve 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

Authors: Hiroshi Yamauchi, Shinya Kagawa, Yoshihiko Kishibe, Masaaki Takahashi, Tatsuya Higashi

Academic affiliation: Division of PET Imaging, Shiga Medical Centre Research Institute, Shiga, Japan

Address correspondence to: Hiroshi Yamauchi, Division of PET Imaging, Shiga Medical Center Research Institute, 5-4-30 Moriyama, Moriyama 524-8524, Japan
Tel: +81-77-582-6034; Fax: +81-77-582-6041
E-mail: yamauchi@res.med.shiga-pref.jp
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 (CMRO$_2$) 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 CMRO$_2$ 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**

**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

**Background and Objectives:** Many cross-sectional studies have shown that chronic hemodynamic impairment may lead to selective cortical neuronal damage in patients with atherosclerotic internal carotid artery or middle cerebral artery occlusion or stenosis. The purpose of this longitudinal study was to clarify the relationship between the progression of cortical neuronal damage and changes in baseline and follow-up hemodynamics evaluated by changes in benzodiazepine receptors (BZRs) as a measure of receptor density.

**Methods:** This study was repeated twice using 11C-flumazenil positron emission tomography (PET) to evaluate 80 patients with treated and non-ischemic atherosclerotic ICA or MCA occlusion or stenosis. The average hemisphere value of hemodynamic parameters obtained from 15O gas PET scans was used to quantitatively study the abnormal reduction of cortical BZR levels and the changes in BZR indexes in the MCA territory. Changes in OEF were also assessed.

**Results:** During the follow-up period (average 26 ± 20 months), 40 patients (50%) showed a rise in the BZR index. Multivariate logistic regression analysis revealed that a rise in the BZR index was associated with a lower baseline cerebral blood flow and a higher oxygen extraction index during follow-up. Higher oxygen extraction index during follow-up was also related to the use of statins.

**Conclusions:** In patients with atherosclerotic ICA or MCA disease, the progression of cortical neuronal damage is related to baseline hemodynamic impairment and hemodynamic deterioration during follow-up. Statin use may be beneficial in preventing hemodynamic deterioration and thus preventing neuronal damage.

**Keywords:** Carotid disease, Cerebral cortex, PET, Prognosis, Risk factors

(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)
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 (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；(4) 药物治疗的患者，在第一次 PET 检查后没有再发卒中或短暂性脑缺血发作；(5) 可以并愿意做随访 PET 检查。

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。

PET 评价

每名受试者均采用先进全身扫描仪 (通用电气医疗系统，沃瓦托萨，WI) 进行 PET 扫描，可实现 35 张间隔 4.25 mm 的图像同时采集。使用

\[
\text{11C-FMZ}
\]
合成

\[
\text{BP(不可置换的)}
\]
作为对照区域

19.2.21。使用

\[
\text{11C-FMZ}
\]
开始 50 min 的动态 PET 扫描。采用稳态法计算脑血流量 (cerebral blood flow, CBF)、脑氧代谢速率 (cerebral metabolic rate of oxygen, CMRO2) 和 OEF。CMRO2 和 OEF 在 CBV 的基础上进行校正。采用动态数据和罗根图形分析根据对照组织计算

\[
\text{11C-FMZ}
\]
的结合潜力 [binding potential, BP(不可置换的)]，把连接部位作为对照区域

19.2.21。随访中 BZR 指数上升

临床特征

<table>
<thead>
<tr>
<th>患者人数</th>
<th>年龄, 年</th>
<th>性别, 人数</th>
<th>责任动脉, 人数</th>
<th>其它身体疾病, 人数</th>
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<td>患者人数</td>
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<td>他汀类药物</td>
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<td>BZR 指数</td>
<td>34.7±32.8°</td>
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<tr>
<td>基线</td>
<td>69.2±59.0°*</td>
<td>17.8±24.5°</td>
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</table>

注：10 例对照组的 BZR 指数为 1.78±1.79。BZR: 苯二氮卓受体；SD: 标准差。*P<0.05 相比最近 BZR 不做提及。
数据分析

O₂ 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神经节和丘脑水平, 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。根据图像 23,10 个图像的 ROI 都覆盖了 MCA 的分布区及外侧边界区域。CMRO₂、OEF、CBV 和 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。对照组指数变化量的平均 ± SD 值是 0.94 ± 1.38。在患者中, 增加量超过正常人 95% 的上限 (平均值 + 2.50SD) 变化量的独立预测价值。对于所有分析, 接受统计学显著性差异为 P<0.05。

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。对于统计学显著性差异, 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, 动脉病变患侧半球, 1 例中患者原存的白质病变进展, 并且 1 例无症状患者的皮质下白质处和 1 例中患者的皮质前部出现点状状病灶增多。在动脉病变对侧半球, 2 例中患者基底节区发现点状状病灶增多。其他 7 例患者随访 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之间差异无显著性 (分别为 3/40 与 2/40; Fisher 精确检验, P>0.99)。

随访的 MR 血管造影结果显示 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 血管造影结果显著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之间有显著性差异 (分别为 6/40 与 0/40; Fisher 精确检验, P=0.025)。

随访的 MR 血管造影结果显示 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 血管造影结果显著显示狭窄程度变化的发生率在随访 BZR 指数增加与不增加的患者人群之间有显著性差异 (分别为 6/40 与 0/40; 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 CBF、CMRO₂、OEF 和 CBF/CBV 值有更高的趋势并接近差异有显著性 (P=0.06), 随访 OEF 变化量更大 (P=0.13)。随访 OEF 的改变与患者基线 OEF 值负相关 (Spearman, 秩相关系数 r=-0.59; P<0.01)。随访 OEF 增量与基线 CBF 值负相关而与随访 OEF 变化量正相关 (图 2)。

采用多元 logistic 回归分析 (逐步向前) 分析基线 CBF、CMRO₂、OEF、CBV 和 CBF/CBV 值及在随访中的变化, 发现基线 CBF 值及随访 OEF 增量可以作为 BZR 指数增加的独立预测因素 (模型 3, 模型 1)。基线 CBF 值及随访 OEF 增量还可以作为纳入首次和随访 PET 间隔后的独立预测因素 (模型 2)。随访 BZR 变量与基线 CBF 值负相关而与随访 OEF 变化量正相关 (图 2)。
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）和由于代谢降低（皮质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 和 BZR 指数的贡献分别为 31.5% 和 14.3%。皮质下缺血病变对相关性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 变化的关联 (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 2 者差异无显著性。BZR 指数在有症状和无症状患者组直接差异无显著性。而 2 组之间 CMRO2、CBV 和 CBF/CBV 值的变化量差异有显著性。

### 讨论

本纵向研究证明了患有动脉粥样硬化性 ICA 或 MCA 病变且随访期间无缺血性卒中发生的患者慢性血流动力学障碍与选择性皮层神经元损伤之间的关联。随访时外形正常的大脑皮层处 BZR 指数升高代表选择性皮层神经元损伤, 并可由基线 CBF 下降或随访 OEF 增加来预测。此外随访期间 OEF 增加最常见于未服用他汀类药物的患者。

对于存在动脉粥样硬化性 ICA 或 MCA 病变的患者, 基线血流动力学障碍可能可以预测进行性选择性皮层神经元损伤及后续缺血性卒中。本研究发现 CBF 降低伴随皮层神经元损伤进展可以通过基线 OEF 和 BZR 指数增加来解释, 这也提示 CBF 下降可能是贫困灌注和皮层代谢下降的反映。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皮层神经元已经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, 尤其是那些有基线贫困灌注的患者。本研究发现皮层神经元损伤进展也随随访 OEF 增加有关, 由于血流动力学恶化。通过校正 CBF 下降的影响后, 随访期间 BZR 指数增加和 OEF 增加显著相关。OEF 变化量与基线 OEF 值负相关, 这表明基线皮层贫困灌注的患者随访 OEF 增加的幅度更大。基线有贫困灌注的患者 OEF 增加时随访下降更多, 从而导致神经元损伤 (在线补充数据图 I)。在基线贫困灌注的患者, OEF 增加的量级较小。为了进一步研究, 我们将基线 OEF 增加和 OEF 增加之间的关系探讨更深入的原因。事实上, 血流动力学恶化对随访时选择性皮层神经元损伤的影响作用对于有/无基线贫困灌注的患者是不同的。

### 自变量 相对危险度 95%CI P 值

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<tr>
<th>自变量</th>
<th>相对危险度</th>
<th>95%CI</th>
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<td>CBF, ml/(100g·min)</td>
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<td>0.0195</td>
</tr>
<tr>
<td>间隔,月</td>
<td>1.017</td>
<td>0.991-1.043</td>
<td>0.2125</td>
</tr>
</tbody>
</table>

**注:** CI: 可信区间; BZR: 苯二氮卓受体; CBF: 脑血流量; CMRO2: 脑氧代谢速率; OEF: 氧摄取指数; PET: 正电子发射断层扫描。

**表 1** 相对危险度

<table>
<thead>
<tr>
<th>参数特征</th>
<th>是</th>
<th>否</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, ml/(100g·min)</td>
<td>32.9±6.7*</td>
<td>36.4±7.5</td>
</tr>
<tr>
<td>CMRO2, ml/(100g·min)</td>
<td>2.97±0.41</td>
<td>3.15±0.41</td>
</tr>
<tr>
<td>OEF, %</td>
<td>50.9±7.5</td>
<td>50.7±5.9</td>
</tr>
<tr>
<td>CBV, ml/100g</td>
<td>3.2±0.56</td>
<td>3.58±0.62</td>
</tr>
<tr>
<td>CBF/CBV, min⁻¹</td>
<td>4.9±1.13</td>
<td>10.39±2.39</td>
</tr>
</tbody>
</table>

**注:** P<0.05 相比于随访 BZR 不增高组。

### 表 2 15O 气体 PET 变量

<table>
<thead>
<tr>
<th>参数特征</th>
<th>增加中 BZR 指数上升</th>
<th>有症状 vs 无症状</th>
<th>无症状 vs 常规对照</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, ml/(100g·min)</td>
<td>31.9±6.7*</td>
<td>23.4±0.40*</td>
<td>23.4±0.40*</td>
</tr>
<tr>
<td>CMRO2, ml/(100g·min)</td>
<td>3.43±0.58</td>
<td>3.52±0.58</td>
<td>4.10±0.58</td>
</tr>
<tr>
<td>OEF, %</td>
<td>53.3±6.4</td>
<td>50.6±5.9</td>
<td>53.9±6.4</td>
</tr>
<tr>
<td>CBV, ml/100g</td>
<td>3.43±0.58</td>
<td>3.52±0.58</td>
<td>3.45±0.58</td>
</tr>
<tr>
<td>CBF/CBV, min⁻¹</td>
<td>9.41±1.68</td>
<td>10.34±2.14</td>
<td>9.41±1.68</td>
</tr>
</tbody>
</table>

**注:** P<0.05 相比于随访 BZR 不增高组。

**表 3 动脉病变患侧半球 BZR 指数增加作为因变量的多元 logistic 回归分析**

<table>
<thead>
<tr>
<th>自变量</th>
<th>相对危险度</th>
<th>95%CI</th>
<th>P 值</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, ml/(100g·min)</td>
<td>0.902</td>
<td>0.839-0.970</td>
<td>0.0057</td>
</tr>
<tr>
<td>OEF 增加, %</td>
<td>1.090</td>
<td>1.014-1.171</td>
<td>0.0195</td>
</tr>
<tr>
<td>间隔,月</td>
<td>1.017</td>
<td>0.991-1.043</td>
<td>0.2125</td>
</tr>
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</table>

**注:** CI: 可信区间; BZR: 苯二氮卓受体; CBF: 脑血流量; OEF: 氧摄取指数。

本研究结果对于临床应用动脉粥样硬化性 ICA 或 MCA 病变引起的皮层神经元损伤是有重要意义的。首先, 在未发生明确卒中事件前, 选择性皮层神经元损伤进展与慢性血流动力学障碍有关。因而, 基线或随访时的血流动力学状态可能对基线的差异没有显著影响。这可能会增加脑缺血风险 1,3,5。因此本研究有理由认为基线贫困灌注与后续缺血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皮层神经元已经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增加选择性皮层神经元损伤风险，尤其是那些有基线贫困灌注的患者。本研究发现皮层神经元损伤进展也随随访 OEF 增加有关, 有基线贫困灌注的患者有更高的风险。通过校正 CBF 下降的影响后, 随访期间 BZR 指数增加和 OEF 增加显著相关。OEF 增加与基线 BZR 值有关, 这表明基线皮层贫困灌注的患者随访 OEF 增加的幅度更大。基线有贫困灌注的患者 OEF 增加时随访下降更多, 从而导致神经元损伤 (在线补充数据图 I)。有基线贫困灌注的患者, 脑血流量的量级较少。为了进一步研究, 我们将基线 OEF 增加和 OEF 增加之间的关系探讨更深入的原因。事实上, 血流动力学恶化对随访时选择性皮层神经元损伤的影响作用对于有/无基线贫困灌注的患者是不同的。

### 表 2 15O 气体 PET 变量

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**注:** P<0.05 相比于随访 BZR 不增高组。
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 降低，这与无 MRI 新病灶的术后认知功能改善相关。皮层下缺血性进展可能由于基底节区受累导致 BZR 下降，而这也反映了其与血流动力学和代谢参数的变化无关。

当前研究中发现皮层下缺血病变的程度与 BZR 指数之间的关系，并没有支持之前的研究。此前的研究没有证明皮层下缺血病变的程度与 BZR 指数之间的关系。

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 扫描分析检测了 CO2 气体用的是经典的 ROI 分析。通过多个层面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的矛盾。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。皮质 FMOV 结合下降可能至少部分反映了由于出血或软化损伤导致的皮质萎缩增加（例如神经元缺失和部分体积效应）以及组织 BZR 增加下降。正常对称群只选取了 10 例健康对照组，且明显比本研究中的患者年轻。此外，随访检查中发现 Z 指数差异无显著性，只在上述 10 例对照个体中的 7 例上进行。

结论

对于动脉粥样硬化性 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。颈动脉 CBF 下降可能反映了早期皮质与皮层下皮质神经元损伤，随着随访 OEF 增加可能反映了血流动力学恶化。为了防止选择性皮层下神经元损伤进展，采用血管重建术改善血流动力学障碍并适时地控制血管危险因素（如，使用他汀类药物）可能是很有用的。

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

Hiroshi Yamauchi, MD, PhD; Shinya Kagawa, MS; Yoshihiko Kishibe, RT, et al.
Division of PET Imaging, Shiga Medical Center Research Institute, Moriyama, Japan

背景および目的：横断的研究では、内頸動脈または大脳動脈のアテローム硬化性閉塞性疾患のある患者における慢性血行力学的障害は選択的な皮質神経損傷を引き起こす可能性があることが示唆されている。本報告的研究は、中樞性ペンゾジアゼピン受容体（BZR）の減少を指標とした皮質神経損傷の進行はベースライン時の血行動態および追跡調査中の血行動態悪化と関連するか否かを検討することを目的とした。

方法：内頸動脈または大脳動脈のアテローム硬化性閉塞性疾患に対して内科治療を行い追跡調査中に虚血性エピソードがない患者80例において、PETと1C-フマルマゼニルを用いて経時的なBZRの分布を2回評価した。3D stereotactic surface projectionsで大脳動脈が分布する範囲内の大脳皮質におけるBZRの異常減少を定量し、BZR指数の変化と18F PETにより求めた血行力学的パラメータの大脳半球平均値との相関性を検討した。

結論：動脈硬化と同様の大脳半球では、追跡調査中（平均26±20ヶ月）に患者40例（50％）でBZR指数が上昇した。多変量ロジスティック回帰解析では、BZR指数の上昇はベースライン時の低動脈血流量および追跡調査中の酸素摘取率の増加と関連することが明らかになった。また、追跡調査中の酸素摘取率の増加はスタチンの非使用と関連した。