Increase in $[^{18}\text{F}]$-Fluoroacetate Uptake in Patients With Chronic Hemodynamic Cerebral Ischemia

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Background and Purpose—$[^{18}\text{F}]$-fluoroacetate ($[^{18}\text{F}]$-FACE) can be used for evaluating glial cell metabolism. Experimental studies have shown an increase in $[^{18}\text{F}]$-FACE uptake in rodent models of cerebral ischemia. The aim of this study was to determine whether $[^{18}\text{F}]$-FACE uptake is increased in the noninfarcted cerebral cortex in patients with hemodynamic ischemia owing to atherosclerotic internal carotid artery or middle cerebral artery disease.

Methods—We evaluated 9 symptomatic patients with unilateral atherosclerotic internal carotid artery or middle cerebral artery disease and no cortical infarction using positron emission tomography with $[^{18}\text{F}]$-FACE and $[^{15}\text{O}]$-gases. $[^{18}\text{F}]$-FACE uptake during 40 to 60 minutes after injection was compared with the cerebral blood flow, cerebral metabolic rate of oxygen, oxygen extraction fraction, and cerebral blood volume in the middle cerebral artery distributions.

Results—Significant decreases of cerebral blood flow and cerebral metabolic rate of oxygen and increases of oxygen extraction fraction and cerebral blood volume were found in the hemisphere ipsilateral to the arterial lesion, and $[^{18}\text{F}]$-FACE uptake in this region was greater than that in the contralateral hemisphere. The relative $[^{18}\text{F}]$-FACE uptake (ipsilateral/contralateral ratio) was negatively correlated with cerebral blood flow or cerebral metabolic rate of oxygen values and was positively correlated with oxygen extraction fraction values. Multivariate analysis showed that the ipsilateral/contralateral $[^{18}\text{F}]$-FACE uptake ratio was independently correlated with the cerebral blood flow (or oxygen extraction fraction) and cerebral metabolic rate of oxygen values.

Conclusions—In patients with atherosclerotic internal carotid artery or middle cerebral artery disease, $[^{18}\text{F}]$-FACE uptake is increased in the noninfarcted cerebral cortex with chronic hemodynamic ischemia characterized by misery perfusion with decreased oxygen metabolism. Increased $[^{18}\text{F}]$-FACE uptake may indicate the cortical regions that are at particular risk for ischemic damage. (Stroke. 2015;46:2669-2672. DOI: 10.1161/STROKEAHA.115.010080.)

Key Words: carotid artery, internal $[^{18}\text{F}]$-fluoroacetates $[^{18}\text{F}]$-FACE infarction $[^{15}\text{O}]$-gases positron-emission tomography stroke

In patients with atherosclerotic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusive disease, the chronic reduction in cerebral perfusion pressure (chronic hemodynamic compromise) increases the risk for cerebral ischemic damage. Thus, understanding the pathophysiology of hemodynamic cerebral ischemia is essential for effective management of patients with atherosclerotic ICA or MCA occlusive disease.

The glia may contribute to the pathophysiology of hemodynamic cerebral ischemia. The $[^{18}\text{F}]$-fluorinated acetate, $[^{18}\text{F}]$-fluoroacetate ($[^{18}\text{F}]$-FACE) has been considered useful for evaluating glial cell metabolism in the central nervous system. $[^{18}\text{F}]$-FACE may accumulate selectively in glial compartments. FACE is metabolized to fluoroacetyl-CoA and then to fluorocitrate, which inhibits aconitase, one of the main enzymes of the mitochondrial tricarboxylic acid cycle. Therefore, $[^{18}\text{F}]$-FACE accumulation ultimately inhibits the tricarboxylic acid cycle, resulting in the accumulation of metabolized substances under aerobic conditions. Thus, the uptake of $[^{18}\text{F}]$-FACE may reflect glial acetate metabolism. Experimental studies using positron emission tomography (PET) have shown an increase in the uptake of $[^{18}\text{F}]$-FACE in rodent models of cerebral ischemia, although the precise mechanism for the increased uptake of $[^{18}\text{F}]$-FACE was not determined.

Because the increased $[^{18}\text{F}]$-FACE uptake was correlated with infarct volumes, these studies have suggested that the increased $[^{18}\text{F}]$-FACE uptake may reflect the brain regions that are most at risk for ischemic damage. However, there has been no evaluation of $[^{18}\text{F}]$-FACE PET in patients with ischemic stroke.

The objective of this study was to determine whether $[^{18}\text{F}]$-FACE uptake is increased in the noninfarcted cerebral cortex.

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cortex in patients with hemodynamic cerebral ischemia caused by atherosclerotic ICA or MCA disease.

Methods

Patients

We recruited 9 consecutive patients with unilateral symptomatic ath-

erosclerotic occlusion or stenosis of the ICA or MCA. They were

referred to our PET unit over a period of 10 months to undergo hemo-
dynamic parameter evaluation as part of a clinical assessment to de-
termin the need for an extracranial-to-intracranial bypass. Inclusion
criteria were as follows: (1) occlusion of the extracranial ICA, or
occlusion or stenosis (>50% diameter reduction) of the intracranial
ICA or MCA, as documented by conventional or magnetic resonance
angiography; (2) ability to independently carry out daily life activities
(modified Rankin scale score <3); and (3) history of completed stroke
involving the relevant ICA or MCA territory. The exclusion criteria
were (1) cortical infarction detectable on routine magnetic resonance
images (T1-weighted, T2-weighted, or FLAIR images); (2) history of
transient ischemic attack or stroke in regions other than the relevant
ICA or MCA territory; (3) history of vascular reconstruction surgery;
(4) contralateral ICA or MCA stenosis (>50%); or (5) presence of
potential sources of cardiogenic embolism.

The patients included 8 men and 1 woman aged 51 to 77 years
(mean±SD, 64±10 years). The interval between the stroke event and
PET evaluation was 70±39 days (range, 17–150 days). The symptom-
atnic qualifying artery occlusion type was extracranial ICA occlusion
in 4 cases, intracranial ICA occlusion in 1 case, MCA occlusion in
2 cases, and MCA stenosis in 2 cases. Magnetic resonance imaging
revealed internal border zone infarction in 4 cases and superficial per-
forator infarction in 5 cases.

The ethics committee of our center approved the study pro-
tocol, and all patients provided written informed consent before participation.

PET Measurements

We performed PET scans using a whole-body Advance scanner
(Generic Electric Medical System; Wauwatosa, WI), which permits
simultaneous acquisition of 35 image slices with interslice spacing
of 4.25 mm. A transmission scan was performed using 68Ga/68Ga for
attenuation correction in each subject before administration of the
tracer. In reconstruction of PET data using filtered back projection,
images were blurred to 6.0 mm, the full width at the half maximum in
the transaxial direction using a Hanning filter.

First, a series of 18O-gas experiments was performed. The sub-
jects continuously inhaled C18O2 and 18O through a mask. The scan
time was 5 minutes. Bolus inhalation of C18O with scanning for 3
minutes was used to measure the cerebral blood volume (CBV).
Arterial samples were manually obtained during the scanning.

After the 18O-gas experiment, an 18F-FACE evaluation was performed.5 Tracer synthesis was initiated with (p-tosyloxy) acetal
eyl ester as a precursor using a distillation procedure. After labeling
the reaction, the reaction mixture was distilled under reduced pres-
sure, trapped with sodium hydroxide, and hydrolyzed. The crude
product was passed through an ion-exchange resin and rinsed with
water, and then 18F-FACE was eluted with 0.9% NaCl. Specific activi-
ties at the time of injection ranged from 58.4 to 103.9 (mean, 81.3)
μGBq/ID represents the injected dose.

Data Analysis

We analyzed 4 tomographic planes from 67.5 to 80.25 mm above
and parallel to the orbitomeatal line, which corresponded to the levels
from the corona radiata to the centrum semiovale. The hemisphere
affected by the ICA or MCA disease is referred to hereafter as the
ipsilateral hemisphere. The region of interest (ROI) was set on the
CBF images. Each image was examined by placing a total of 10 to
12 circular ROIs, 16 mm in diameter each, compactly over the gray
matter of the outer cortex in each hemisphere. According to the atlas,
the ROIs in all 4 images covered the distribution of the MCA as well
as the possible border zone areas.6 The same ROIs were transferred
to the other images. The mean hemispheric values were calculated as
the average of the values of all circular ROIs. To control the effect of
fluctuations in whole-brain values and to determine the independent
effect of ICA or MCA disease on the change, we analyzed the ipsilat-
eral/contralateral ratio of the 18F-FACE uptake.

Statistical Analysis

We compared the results in each cerebral hemisphere using the
Wilcoxon signed-rank test. Spearman rank correlation was used to
analyze the relationship between the ipsilateral/contralateral
18F-FACE uptake ratio, and the CBF, CMRO 2, OEF, and CBV values.
Stepwise multiple linear regression analysis was used to test
the independent predictive value of the hemodynamic variables with
respect to the ipsilateral/contralateral 18F-FACE uptake ratios. In all
analyses, a P value of <0.05 was regarded as indicating statistical
significance.

Results

For all subjects, significant decreases of CBF, CMRO 2, and
CBF/CBV and increases of OEF and CBV were found in the cerebral
cortex ipsilateral to the arterial lesion, and

18F-FACE uptake (standardized uptake value) was greater in
this region than that in the contralateral cortex (Table). The rela-
tive 18F-FACE uptake (ipsilateral/contralateral ratio) was
negatively correlated with the CBF or CMRO 2 values and
was positively correlated with OEF values (Figures 1 and 2).
No correlation was found between relative 18F-FACE uptake and
CBV. The CBF values were strongly correlated with
OEF values (r=−0.90, P=0.011). There was no correlation
between relative 18F-FACE uptake and the time elapsed from
symptoms.

Stepwise linear regression analysis (forward selec-
tion), including CBF, CMRO 2, OEF, CBV, CBF/CBV, and

<table>
<thead>
<tr>
<th>Table.</th>
<th>Positron Emission Tomography Values (Mean±SD) in the Hemispheres Ipsilateral and Contralateral to the Artery Disease</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>CBF, mL/100 g per min</td>
<td>28.9±5.2*</td>
</tr>
<tr>
<td>CMRO 2, mL/100 g per min</td>
<td>2.83±0.44†</td>
</tr>
<tr>
<td>OEF, %</td>
<td>54.3±9.2†</td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>3.81±0.57†</td>
</tr>
<tr>
<td>CBF/CBV, per min</td>
<td>7.76±1.48*</td>
</tr>
<tr>
<td>18F-FACE (SUV)</td>
<td>1.47±0.19*</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; CBV, cerebral blood volume; CMRO 2, cerebral metabolic rate of oxygen; 18F-FACE, 18F-fluorooxocetate; OEF, oxygen extraction fraction; and SUV, standardized uptake value.

* P<0.01 and † P<0.05 vs corresponding value in the contralateral hemisphere (Wilcoxon signed-rank test).
patient age produced a model (correlation coefficient of 0.94, \( P < 0.0001 \)) for the relative \(^{18}\text{F}\)-FA uptake that included only CBF and CMRO\(_2\) as significant factors contributing to the correlation. CBF was the most heavily weighted factor and accounted for 75.8% of the variation in the change of relative \(^{18}\text{F}\)-FA uptake, whereas CMRO\(_2\) accounted for 12.4% of the variation. In the multiple regression model, CBF and CMRO\(_2\) were independently and negatively correlated with relative \(^{18}\text{F}\)-FA uptake.

Discussion

To our knowledge, this is the first study that shows the increase of \(^{18}\text{F}\)-FA uptake in patients with hemodynamic cerebral ischemia caused by atherosclerotic ICA or MCA disease. Increased \(^{18}\text{F}\)-FA uptake in the noninfarcted cerebral cortex was primarily associated with decreased CBF and increased OEF. Decreased CMRO\(_2\) also contributed to the increase of \(^{18}\text{F}\)-FA uptake. Therefore, increased \(^{18}\text{F}\)-FA uptake was associated with chronic hemodynamic cerebral ischemia characterized by misery perfusion with decreased oxygen metabolism.

We could not determine the direct or specific mechanism of the observed increase of \(^{18}\text{F}\)-FA uptake in the ischemic tissue in the present study. Previous experimental studies have shown an increase in the uptake of \(^{18}\text{F}\)-FA in rodent models of acute cerebral ischemia or ischemia–hypoxia. Marik et al\(^4\) reported that after transient MCA occlusion (90 minutes) in the rat brain, elevated uptake of \(^{18}\text{F}\)-FA at 24 hours could depict the ischemic territory and was correlated with infarct volumes at 48 hours and with the presence of activated astrocytes around the infarcted tissue at 24 hours. Based on these results, the authors suggested that elevated \(^{18}\text{F}\)-FA uptake may reflect increased glial metabolism because of activation in response to the insult. However, in a PET study using a rat model of transient MCA occlusion (60 minutes), increased \(^{18}\text{F}\)-FA uptake was not associated with increased \(^{11}\text{C}\)-PK11195 uptake, an indicator of glial activation.\(^9\) Another PET study investigated \(^{18}\text{F}\)-FA kinetics in rodent models of cerebral hypoxia–ischemia at 3 and 24 hours post insult; \(^{18}\text{F}\)-FA uptake in the lesion with T2 elongation was significantly higher at 30 minutes post injection.\(^10\) Kinetic modeling showed that the elevated \(^{18}\text{F}\)-FA uptake was primarily transport-driven (an increase in \(K_1/k_2\) with decreased \(k_2\)) rather than metabolism-driven (changes in \(k_3\)). Therefore, increased \(^{18}\text{F}\)-FA uptake may not reflect increased metabolism in the activated glial cells but rather \(^{18}\text{F}\)-FA retention (decreased \(k_2\)) under conditions of metabolic derangement.
or neuronal damage caused by ischemia. The association of increased $^{18}$F-FACE uptake with decreased oxygen metabolism in the region with misery perfusion observed in the present study supports this speculation. No change of $^{18}$F-FACE uptake was found in the contralateral cerebellum showing decreased CBF and CMRO$_2$ caused by functional deactivation (data not shown), which indicates that $^{18}$F-FACE uptake is not simply dependent on CBF or CMRO$_2$. Experimental studies in our laboratory are ongoing for further clarification of the molecular mechanisms driving $^{18}$F-FACE retention, which may lead to the development of new therapeutic strategies for ischemic tissue damage.

In conclusion, $^{18}$F-FACE uptake was increased in the noninfarcted cerebral cortex in patients with chronic hemodynamic cerebral ischemia characterized by misery perfusion with decreased oxygen metabolism. Our study was limited by small sample size with a mixture of ICA and MCA disease and by lack of data on reproducibility. In addition to the clarification of the mechanism for the increased uptake of $^{18}$F-FACE using animal experiments or other modalities of imaging (eg, magnetic resonance imaging), follow-up studies should be performed to determine whether increased $^{18}$F-FACE uptake indicates the cortical regions that are most at risk for tissue damage owing to misery perfusion and whether $^{18}$F-FACE-PET imaging is useful to select patients who need immediate treatments.

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Disclosures
None.

References
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