Cerebral Hemodynamic Evaluation Using Perfusion-Weighted Magnetic Resonance Imaging
Comparison With Positron Emission Tomography Values in Chronic Occlusive Carotid Disease

Katsufumi Kajimoto, MD; Hiroshi Moriwaki, MD; Naoaki Yamada, MD; Kohei Hayashida, MD; Junya Kobayashi, MD; Kotaro Miyashita, MD; Hiroaki Naritomi, MD

Background and Purpose—Perfusion-weighted magnetic resonance imaging (PWI) is a reliable and semiquantitative method for estimating cerebral hemodynamics. We sought to evaluate the potential of PWI for assessing cerebral blood flow (CBF) and metabolism compared with positron emission tomography (PET) in patients with chronic occlusive carotid disease.

Methods—In 24 patients with chronic unilateral occlusive carotid disease, time-to-peak (TTP) delay (TTP-D) measured by PWI was compared with CBF, cerebral blood volume (CBV), and oxygen extraction fraction (OEF) obtained by PET. TTP indicates the time from the start of PWI to the bolus peak. TTP-D indicates the difference in TTP values between the occlusive and contralateral hemispheres. TTP-D was compared between patients with normal and reduced CBF/CBV and also between patients with normal and elevated OEF.

Results—TTP-D in patients with reduced CBF/CBV was significantly longer than that in patients with normal CBF/CBV (3.4±1.8 versus 1.4±0.7 seconds; P=0.001). In the patients with reduced CBF/CBV, TTP-D correlated with OEF significantly (r=0.710, P<0.0001). TTP-D in patients with elevated OEF was significantly longer than that in patients with normal OEF (4.8±2.2 versus 2.0±0.9 seconds; P<0.01). In all 5 patients with TTP-D ≥4 seconds, OEF was elevated markedly.

Conclusions—TTP-D ≥4 seconds is considered to indicate a high risk of hemodynamic failure. The measurement of TTP-D by PWI appears to provide important clinical information for evaluating cerebral hemodynamics in chronic occlusive carotid disease. (Stroke. 2003;34:1662-1666.)

Key Words: carotid artery occlusion • hemodynamics • magnetic resonance imaging, perfusion-weighted • tomography, emission computed

Perfusion-weighted magnetic resonance imaging (PWI) provides information on the hemodynamic status of tissue and can detect impaired perfusion in both the ischemic core and the surrounding brain regions.1 Quantification of cerebral blood flow (CBF) and cerebral blood volume (CBV) with PWI is enabled by applying indicator dilution theory.2–7 However, the indicator dilution method requires measurements of the arterial contrast agent concentration as an arterial input function (AIF), which is a demanding and complicated process in the daily clinical setting. Time-to-peak (TTP) value can be estimated readily and rapidly with PWI. TTP images further permit us to obtain another hemodynamic parameter, TTP delay (TTP-D), which is the difference between the TTP in the target hemisphere and in the contralateral hemisphere.

Several studies compared results of PWI and those of established hemodynamic imaging techniques.5,6,8–10 To the best of our knowledge, however, there have been no clinical studies comparing PWI with positron emission tomography (PET), a gold standard of perfusion imaging technique, in chronic occlusive carotid disease.

The aim of this study was to evaluate the potential of TTP-D for assessing cerebral hemodynamics, including cerebral metabolism, in comparison with PET parameters in patients with chronic occlusive carotid disease. We chose stroke patients with chronic unilateral carotid occlusive disease as our subjects because they offer a stable experimental population.

Subjects and Methods

Subjects
Between June 2000 and May 2002, a total of 37 consecutive patients with chronic cerebrovascular diseases were examined with both PWI and PET in the same period in our department (Department of...
**Patient Characteristics, MRA, and Angiographic Findings**

<table>
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R indicates right; L, left; IC, internal carotid artery occlusion; ICS, internal carotid artery stenosis; MCO, middle cerebral artery occlusion; MCS, middle cerebral artery stenosis; TIA, transient ischemic attack.

**MRI Protocol**

MRI was performed with the use of a clinical 1.5-T whole-body MR system with a conventional gradient system (Magnetom Vision, Siemens Medical System). Before PWI studies, conventional MR images, including T2-weighted, T1-weighted, and fluid-attenuated inversion recovery (FLAIR) images, were acquired with a spin-echo pulse sequence. PWI was acquired with T2*-weighted imaging; gradient-echo, echo-planar imaging had the following parameters: slice number 10, slice thickness 4 mm, repetition time 2000 ms, echo time 60 ms, field of view 230 mm, and matrix 128×128. PWI was repeated 40 times every 2 seconds. A contrast agent of 0.1 mmol/kg gadolinium-DTPA was injected through an antecubital vein with a 22-gauge cannula at a rate of 3 to 4 mL/s followed by 20 mL saline. All images including TTP were calculated automatically on the host computer of the MR system. TTP refers here to the time between the start of PWI and the bolus peak. TTP-D was calculated as TTP in the occlusive hemisphere subtracted from that in the contralateral hemisphere.

**PET Protocol**

PET measurements were performed during the same period as MRI in all the patients. CBF, CBV, cerebral metabolic rate for oxygen (CMRO2), and oxygen extraction fraction (OEF) were obtained with a Headtome IV PET scanner (Shimadzu) with a spatial resolution of 4.5 mm full width at half maximum and the 15O-labeled gas inhalation technique. In brief, an emission scan with an external 96Ge-68Ga ring source was corrected for the effects of tissue attenuation with the use of corresponding transmission scans. After transmission scanning, the separate scans were performed during continuous inhalation of 15O-labeled carbon dioxide (C15O2) and molecular oxygen (16O2) for the measurements of CBF and OEF, respectively. The third scan, for the measurement of CBV, was performed after 2-minute inhalation of 15O-labeled carbon monoxide (C15O). During the scans, blood samples were obtained serially for measuring arterial isotope activities, arterial oxygen content (O2C), and arterial Pco2. CMRO2 was calculated as CBF×OEF×O2C.

**Data Analysis**

Two planes, including the basal ganglia and centrum semiovale, were chosen for analyses of PWI and PET data. On each imaging plane, circular ROIs with 16-mm diameters were placed manually on the MCA area of the occlusive hemisphere. ROIs are also placed in the homologous regions of the contralateral MCA area to calculate TTP-D. R indicates right; L, left.
values $\geq 0.52$, the mean plus 2 SD of normal values, were cited to indicate abnormally elevated OEF.

### Statistical Analysis

Results are presented as mean $\pm$ SD. Relations between TTP-D obtained by PWI and CBF/CBV obtained by PET were evaluated with linear regression analysis. Relations between TTP-D obtained by PWI and OEF obtained by PET were evaluated with logarithmic regression analysis. Relations between TTP-D obtained by PWI and CBF/CBV obtained by PET were evaluated with logistic regression analysis. Statistical Analysis

**Results**

In a representative case, a 50-year-old man (patient 1) developed left hemiparesis and dysarthria. DSA demonstrated right ICA occlusion. FLAIR images revealed subcortical infarctions in the right centrum semiovale and frontal white matter. PWI showed delayed perfusion throughout the right hemisphere. The mean TTP-D value in the right hemisphere was markedly prolonged to 5.3 seconds. PET demonstrated decreased CBF, elevated OEF, and reduced CBF/CBV in the right hemisphere. PWI showed delayed perfusion in the entire territory of the right (R) hemisphere, with a mean TTP-D of 5.3 seconds. PET demonstrated decreased CBF, elevated OEF, and reduced CBF/CBV in the right hemisphere. The mean TTP-D value in the right hemisphere. L indicates left.

In this study we evaluated the usefulness of TTP-D measurements by PWI as a tool of cerebral hemodynamic estimation.

**Discussion**

In this study we evaluated the usefulness of TTP-D measurements by PWI as a tool of cerebral hemodynamic estimation.

![Figure 2](image2.png)

**Figure 2.** PWI and PET findings in patient 1 with right ICA occlusion. PWI shows delayed perfusion in the entire territory of the right (R) hemisphere, with a mean TTP-D of 5.3 seconds. PET demonstrates decreased CBF, elevated OEF, and reduced CBF/CBV in the right hemisphere. L indicates left.

![Figure 3](image3.png)

**Figure 3.** Relation between TTP-D and CBF/CBV in 140 ROIs. A significant correlation is observed between the 2 parameters ($r=0.441; P<0.001; n=140$). The patients were also classified into another 2 groups by reduced CBF/CBV ($0.52$) and group $B$ ($0.52$). The mean hemispheric CBF/CBV: group $A$ ($n=9$) with normal CBF/CBV ($10.8$) and group $B$ ($n=6$) with elevated OEF ($8.17$; group $B$ was significantly prolonged compared with that in group $A$ (4.8 seconds; $P<0.001$)).

![Figure 4](image4.png)

**Figure 4.** Comparisons of TTP-D between groups with normal CBF/CBV and reduced CBF/CBV (A) and between groups with normal OEF and elevated OEF (B). A, TTP-D in group $B$ (reduced CBF/CBV; $n=15$) is significantly longer than that in group $A$ (normal CBF/CBV; $n=9$). B, TTP-D in group $B$ (elevated OEF; $n=6$) is significantly longer than that in group $A$ (normal OEF; $n=18$).
in patients with unilateral occlusive carotid disease. TTP-D correlated significantly with PET parameters, such as CBF/ 
CBV and OEF. TTP maps are often used for volumetric analyses because the mappings can demonstrate areas of 
perfusion deficits most distinctively. TTP values, however, are difficult to compare between individuals because the time 
from the intravenous injection to the bolus arrival at the 
cerebral arteries varies greatly between patients.16 Our 
approach to circumvent this problem was to calculate TTP-D; 
this is achieved simply by subtracting the bolus arrival time in 
the contralateral hemisphere from that in the occluded hemi-
sphere. If done in a standardized fashion, the interobserver 
agreement of this method is good and requires minimal 
postprocessing.

Quantitative evaluations of CBF and CBV are enabled by 
PWI with the use of various techniques, such as the indicator dilution method with AIF or the arterial spin labeling meth-
od.17 The former method requires determination of AIF 
and subsequent deconvolution techniques demanding a high 
level of operator intervention and relatively time-consuming 
postprocessing. Furthermore, it remains controversial 
whether ICA or MCA is more suitable as a source of AIF. In 
addition to the shape of the injected bolus, AIF depends on 
cardiac output, vascular geometry, and cerebral vascular 
resistance. The latter method, arterial spin labeling, was 
confirmed to be useful for evaluating the hemodynamics in 
acute stroke because the results obtained are potentially 
quantitative.18 However, there are still technical problems to 
be solved in this technique. The main advantages of using 
TTP-D to evaluate tissue perfusion are the feasibility of 
techniques, the requirement of minimal postprocessing time, 
and the capability of demonstrating abnormal regions 
distinctively.

Ostergaard et al5,6 compared absolute CBF and CBV values obtained by PWI and those measured by PET in 6 
healthy volunteers and experimental pigs. However, there 
have been few direct comparisons between PWI and estab-
lished perfusion imaging techniques in clinical ischemic stroke.9–10 Kikuchi et al10 compared CBF and CBV measured 
by PWI using the indicator dilution method and cerebral 
perfusion reserve estimated by xenon-133 single-photon 
emission CT (SPECT) with acetazolamide in 8 patients with 
chronic occlusive carotid disease. CBF values measured by 2 
methods were closely correlated with each other, yet the 
resolution of PWI was superior to that of SPECT. Further-
more, PWI provided important clinical information for eval-
uating the degree of perfusion reserve impairment. Barber et 
al9 compared hyperperfusion volumes determined by CBF, 
CBV, and mean transit time maps of PWI and those estimated 
with 99mTc-hexamethylpropyleneamine oxime (HMPAO) 
SPECT in 17 chronic stroke patients. PWI maps were found 
to delineate peri-infarct hypoperfusion areas similar to 99mTc-
HMPAO SPECT. Hagen et al10 compared CBF measured by 
PWI and xenon CT in 10 patients. CBF values measured by 
the 2 methods were closely correlated with each other, and 
the resolution of PWI was as high as that of xenon CT. Thus, 
PWI using the indicator dilution method makes it possible to 
estimate the degree of hypoperfusion with high reliability. 
However, no information concerning cerebral metabolism is 
available with the indicator dilution measurement of PWI.

To the best of our knowledge, there has been no clinical 
study comparing TTP-D obtained by PWI and PET param-
eters. Several studies reported that TTP-D measured in the 
acute phase of stroke correlated well with clinical outcome.19–21 Beaulieu et al20 and Neumann-Haefelin et al21 reported that TTP-D had significant correlations with stroke 
volume and clinical outcome scores.

In the present study 13 of 15 patients with TTP-D ≥2 
seconds showed a reduction of CBF/CBV as estimated by 
PET. CBF/CBV is a sensitive marker of perfusion pressure22 
and may be reduced even in cases of a modest decrease of 
perfusion pressure, such as those of the oligemic state. 
Therefore, TTP-D may be useful for detecting areas of low 
perfusion pressure that are viable but at risk of infarction.

One of the most reliable indicators of hemodynamic 
impairment is misery perfusion, which is characterized by 
elevated OEF with the use of PET. According to a study by 
Yamauchi et al23 in 40 patients with symptomatic ICA or 
MCA occlusive disease, increased OEF was an independent 
predictor of 5-year risk of subsequent stroke. With our 
semiquantitative approach, we were able to identify patients 
with OEF elevation as those with TTP-D ≥4 seconds. The 
cutoff of TTP-D at 4 seconds provided good specificity (96% 
for regional values and 100% for mean values) and high 
sensitivity (79% for regional values and 83% for mean 
values) for evaluating OEF elevation. These specificity and 
sensitivity values for the detection of OEF elevation are 
comparable to those of 123I-iodoamphetamine SPECT. 
Imaizumi et al24 studied the capability of split-dose 123I-
iodoamphetamine SPECT for detecting OEF elevation in 27 
patients with chronic carotid occlusive disease on the basis of 
comparisons with PET parameters. The specificity and 
sensitivity for the detection of OEF elevation were 96% and 
82%, respectively. Measurements of TTP-D in chronic ische-
mic stroke therefore may enable detection of patients with 
a high risk of ischemic stroke and selection of candidates for 
further investigation of cerebral circulation with considerably 
high reliability.

There are several limitations of the hemodynamic eval-
uation with TTP-D. First, TTP-D is a semiquantitative and 
indirect measure of tissue perfusion that is obtained on the 
basis of comparison of 2 hemispheric parameters. The exis-
tence of occlusive changes in both cerebral hemispheres 
likely complicates interpretation of results obtained by this 
method. Therefore, we excluded patients with bilateral ca-

![Figure 5. Relation between TTP-D and OEF in 80 ROIs with reduced CBF/CBV. A significant positive correlation is found between the 2 parameters (r=0.710, P<0.0001; n=80).](http://stroke.ahajournals.org/DownloadedFrom)
rotid artery diseases from the present study to obtain a simple experimental population. This, however, does not necessarily mean that TTP-D measurement is meaningless in cases of bilateral carotid artery diseases. A similar TTP-D study in patients with bilateral carotid occlusive diseases should be performed in the future to elucidate the validity of TTP-D measurements in bilateral carotid artery diseases. Second, since contrast media must be administered as a bolus, imaging can be performed only once per imaging session in a first-pass bolus study. Therefore, the quality of the study depends on the administration of a bolus, which requires good venous access.

PWI is a reliable and noninvasive method, available even in outpatients, to assess changes in cerebral perfusion with unilateral carotid occlusion. This MR technique permits monitoring of longitudinal hemodynamic changes, while the conventional MR technique provides high-resolution and high-contrast anatomic information simultaneously. TTP-D can be used to select patients who are candidates for extensive evaluation of vascular lesions by conventional angiography and cerebral hemodynamics by SPECT or PET. PWI is noninvasive, is relatively inexpensive compared with PET or SPECT, and is a simple method that requires less than a few minutes of scanning time. If the present findings can be confirmed in a larger patient sample, TTP-D may be used for selection of specific therapy, such as thrombolytic or neuroprotective therapy in acute stroke and extracranial-intracranial bypass surgery in chronic stroke.

Acknowledgments
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References
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