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

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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 \pm 1.8 versus 1.4 \pm 0.7 seconds; \( P < 0.001 \)). In the patients with reduced CBF/CBV, TTP-D correlated 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 \pm 2.2 versus 2.0 \pm 0.9 seconds; \( P < 0.01 \)). In all 5 patients with TTP-D \( \geq 4 \) seconds, OEF was elevated markedly.

Conclusions—TTP-D \( \geq 4 \) 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
Cerebrovascular Medicine. From these patients, 24 patients (19 men and 5 women; mean age, 68.9 ± 8.2 years; age range, 50 to 83 years) meeting the following criteria were selected as subjects studied: (1) major cerebral artery, such as the internal carotid artery (ICA) or the main trunk of the middle cerebral artery (MCA), is occluded or narrowed (>75%) unilaterally; and (2) vascular lesion is atherosclerotic in nature. The other 13 patients were excluded from the study because of the following reasons: (1) the major cerebral arteries in the contralateral hemisphere were also occluded or narrowed (>50%)(n = 50%); (2) stenosis of the affected side was not sufficiently severe in degree (<75%)(n = 7); or (3) the vascular lesions were attributable to nonatherosclerotic diseases, such as moyamoya disease (n = 2). Sixteen patients had unilateral ICA occlusion, 3 had unilateral ICA stenosis, 4 had unilateral MCA (M1) occlusion, and 1 had unilateral MCA (M1) stenosis (Table). All patients were evaluated >4 weeks after the latest clinical episode. Vascular lesions were evaluated by digital subtraction angiography (DSA) in 12 patients and by MR angiography in the other 12 patients. Thirteen patients had minor stroke, 5 had transient ischemic attack (TIA), and 6 were asymptomatic. The definitions of TIA and minor stroke were based on standardized criteria. TIA was diagnosed clinically in patients with focal neurological symptoms relating to focal cerebral, brain stem, or retinal ischemia with abrupt onset and complete resolution within 24 hours. Minor completed stroke was defined as Rankin Scale score 1 or 2. All patients underwent PWI and PET in the same period (interval, 0 to 12 days; mean, 3.5 ± 3.1 days). There were no symptomatic changes in any patients during the period between PWI and PET. Informed consent was obtained from all patients after a detailed explanation of the purpose of the study and the scanning procedure was provided.

MRI Protocol
MRI was performed with the use of a clinical 1.5-T whole-body MR system with a conventional gradient system (Magnemot 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 mLs 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 Ge⁴ 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 monoxide (C⁵O₂) and molecular oxygen (¹⁸O₂) 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 (C⁵O₂). 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 are placed manually in 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±SD. Relations between TTP-D obtained by PWI and CBF/CBV obtained by PET were evaluated with logarithmic regression analysis. Relations between TTP-D obtained by PWI and OEF obtained by PET were evaluated with linear regression analysis. The patients were divided into 2 groups by the mean hemispheric CBF/CBV: group A \((n=9)\) with normal CBF/CBV \((>10.8)\) and group B \((n=15)\) with reduced CBF/CBV \((\leq 10.8)\). The patients were also classified into another 2 groups by the mean hemispheric OEF: group \( \alpha \) \((n=18)\) with normal OEF \((<0.52)\) and group \( \beta \) \((n=6)\) with elevated OEF \((\geq 0.52)\). The difference in the TTP-D between groups A and B or between groups \( \alpha \) and \( \beta \) was analyzed with a Mann-Whitney U test. A probability value of \( <0.05 \) was considered significant.

**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. L indicates left.

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As shown in the Table, the occlusive hemisphere was supplied by anterograde collateral circulation via the anterior or posterior communicating artery in 15 of 16 patients with ICA occlusion. Retrograde circulation via leptomeningeal arteries was observed in 1 patient with ICA occlusion and in all 4 patients with MCA occlusion.

Figure 3 shows the relation between TTP-D and CBF/CBV in all 140 ROIs. A significant correlation is observed between the 2 parameters \((r=0.441; P<0.001; n=140)\).

In the analysis of all 140 ROIs, TTP-D correlated significantly with OEF \((r=0.576, P<0.0001)\). However, in the analysis of 60 ROIs with normal CBF/CBV alone, TTP-D showed no significant correlation with OEF. In the analysis of 80 ROIs with reduced CBF/CBV alone, a strong positive correlation was observed between TTP-D and OEF \((r=0.710, P<0.0001)\) (Figure 5). TTP-D in group \( \beta \) was significantly longer than that in group \( \alpha \) \((4.8±2.2\) versus \(2.0±0.9\) seconds; \(P<0.01\) ) (Figure 4B). In 5 patients with TTP-D \( \geq 4\) seconds, OEF was elevated to an abnormal extent. The cutoff of TTP-D at 4 seconds provided good specificity \((96\%, 108/112\) ROIs; \(100\%, 18/18\) patients) and high sensitivity \((79\%, 22/28\) ROIs; \(83\%, 5/6\) patients) for evaluating elevated OEF. There was no difference in TTP-D between the patients with anterograde collateral circulation and those with retrograde circulation.

**Discussion**

In this study we evaluated the usefulness of TTP-D measurements by PWI as a tool of cerebral hemodynamic estimation...
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. 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 hemisphere. 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 method. 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. 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 al. 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 established perfusion imaging techniques in clinical ischemic stroke. Kikuchi et al. 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. Furthermore, PWI provided important clinical information for evaluating the degree of perfusion reserve impairment. Barber et al. compared hypoperfusion 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 al. 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 parameters. Several studies reported that TTP-D measured in the acute phase of stroke correlated well with clinical outcome. Beaulieu et al. and Neumann-Haefelin et al. 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 pressure 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 al. 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 al. 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 ischemic 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 evaluation 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 existence of occlusive changes in both cerebral hemispheres likely complicates interpretation of results obtained by this method. Therefore, we excluded patients with bilateral ca-
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.

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