Quantitative Assessment of Cerebral Hemodynamics Using Perfusion-Weighted MRI in Patients With Major Cerebral Artery Occlusive Disease

Comparison With Positron Emission Tomography

Hidehiko Endo, MD; Takashi Inoue, MD; Kuniaki Ogasawara, MD; Takeshi Fukuda, MD; Yoshiyuki Kanbara; Akira Ogawa, MD

Background and Purpose—Cerebrovascular reactivity (CVR) to acetazolamide is a key parameter in determining the severity of hemodynamic impairment in patients with major cerebral artery occlusive disease. Perfusion-weighted MRI (PW MRI) can measure the cerebral blood volume (CBV) as an indicator of hemodynamic impairment. CBV measured by PW MRI was compared with CVR measured by positron emission tomography (PET).

Methods—Twelve normal subjects and 17 patients with major cerebral artery occlusive disease underwent PW MRI and PET. The images were coregistered with 3-dimensional spoiled gradient-recalled acquisition images. Quantitative PW MRI-CBV maps were generated using the indicator dilution method with arterial input function. One large cortical region of interest for each unilateral middle cerebral artery territory was determined on each image. PET-CVR was calculated by measuring cerebral blood flow before and after acetazolamide challenge.

Results—A significant negative correlation was observed between PW MRI-CBV and PET-CVR ($r = -0.713; P < 0.0001$). PW MRI-CBV higher than the mean +2 SD obtained in normal subjects (15.2 mL/100 g) was defined as elevated and PET-CVR lower than the mean −2 SD obtained in normal subjects (15.1%) was defined as reduced. Assuming the PET-CVR as the true determinant of hemodynamic impairment, PW MRI-CBV provided 80.0% sensitivity and 91.7% specificity, with 80.0% positive predictive value for detecting patients with reduced CVR.

Conclusions—The PW MRI-CBV method can simply and accurately identify patients with hemodynamic impairment without exposure to ionizing radiation. (Stroke. 2006;37:388-392.)

Key Words: cerebral blood volume • magnetic resonance imaging • perfusion-weighted imaging

Regional cerebral blood flow (CBF) is at first maintained by dilation of precapillary resistance vessels as local cerebral perfusion pressure falls, which is known as cerebrovascular autoregulation.¹² Some vasodilatory property of vessels can be detected by measurement of CBF at rest and after vasodilatory stimulus such as CO₂ inhalation or acetazolamide administration.³⁴ Quantitative assessment of cerebrovascular reactivity (CVR) to acetazolamide could determine the severity of hemodynamic impairment in patients with major cerebral artery occlusive disease.⁵⁶ Such dilation of precapillary resistance vessels also increases the cerebral blood volume (CBV).² Therefore, reduction of CVR and increase in CBV may be initial indicators of a fall in cerebral perfusion pressure.² Positron emission tomography (PET) is the most reliable method for measuring such hemodynamic changes. However, PET is not widely used clinically because of the high cost and limited availability, so the establishment of other methods is desirable.

MRI can detect the changes in susceptibility during the passage of a compact bolus injection of contrast agent and so provide information about the pattern of brain perfusion.⁷ This method of perfusion-weighted MRI (PW MRI) initially yielded only relative hemodynamic values because of the complexity of susceptibility changes.⁸⁹ Recently, additional postprocessing steps have been developed for deriving quantitative values from PW MRI.¹⁰⁻¹⁴

The present study tried to validate the accuracy of PW MRI for detecting hemodynamic impairment by correlating CBV measured by PW MRI with CVR measured by PET in patients with unilateral major cerebral artery occlusive disease.

Methods

Subjects
This study evaluated 12 male age-matched normal subjects aged 28 to 72 years (mean 62 years) who underwent screening of health
status including medical review of past history, physical examination, and neurological and mental tests. Subjects with a past history of hypertension, diabetes mellitus, atrial fibrillation, or pulmonary disease were excluded. MRI was performed to exclude subjects with organic lesions of the brain. Subjects with leukaemiasis or asymptomatic lacunar infarction were also excluded.

Patients
This study also included 17 patients (4 women and 13 men) aged 24 to 76 years (mean 63 years) with unilateral major cerebral artery occlusive disease (Table 1). All patients had experienced the last cerebral ischemic event more than 2 months before entry into the study. Conventional MRI was performed in all patients. No cortical infarction was observed in any of the patients. Five patients had transient ischemic attacks (1 patient) or without (4 patients) definite cerebral infarction on MRI. Cerebral angiography with arterial catheterization or MR angiography demonstrated internal carotid artery (ICA) stenosis in 2 patients, ICA occlusion in 8 patients, middle cerebral artery (MCA) stenosis in 4 patients, and MCA occlusion in 3 patients. No patient had occlusion or stenosis of more than 50% in the contralateral ICA or MCA.

The study protocol was approved by the local ethical committee. All patients and subjects gave written informed consent before the study.

MRI Protocol
MRI was performed using a GE Signa 3.0 Tesla imager (GE Medical Systems) with a standard head coil. After a sagittal scout image was taken, 3-dimensional spoiled gradient-recalled acquisition (3D SPGR) was acquired for coregistration between PET and PW MRI. A spin echo type echo planar–imaging sequence was used for PW MRI with repetition time 1500 ms, echo time 30 ms, field of view 240 mm, matrix 128×128, 5 slices with 7 mm thickness, and 60 images in each of the 5 slices. In all experiments, a bolus injection of 12 mL gadodiamide (Gd-DTPA-BMA; OMNISCAN, Nycomed Systems) with a standard head coil. After a sagittal scout image was taken, 3-dimensional spoiled gradient-recalled acquisition (3D SPGR) was acquired for coregistration between PET and PW MRI. A spin echo type echo planar–imaging sequence was used for PW MRI with repetition time 1500 ms, echo time 30 ms, field of view 240 mm, matrix 128×128, 5 slices with 7 mm thickness, and 60 images in each of the 5 slices. In all experiments, a bolus injection of 12 mL gadodiamide (Gd-DTPA-BMA; OMNISCAN, Nycomed Imaging) was given at 3 mL/s followed by a 20 mL saline flush using an MR-compatible power injector. The total imaging time was 90 seconds after initiation of the bolus injection. Immediately after MRI, arterial blood sampling was performed to measure $\text{PaCO}_2$, $\text{PaO}_2$, and the blood pH. The PW MRI was performed before the PET study, both on the same day, in all patients.

Table 1. Summary of Clinical Findings in 17 Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Angiographical Findings</th>
<th>Type of Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Rt ICA stenosis</td>
<td>Lacunar</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>F</td>
<td>Minor complete stroke</td>
<td>Rt ICA stenosis</td>
<td>Lacunar</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Lt ICA occlusion</td>
<td>Lacunar</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Lt ICA occlusion</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Lt ICA occlusion</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>TIA</td>
<td>Lt ICA occlusion</td>
<td>Lacunar</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>TIA</td>
<td>Rt ICA occlusion</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Rt ICA occlusion</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>M</td>
<td>TIA</td>
<td>Rt ICA occlusion</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Rt ICA occlusion</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>F</td>
<td>TIA</td>
<td>Lt MCA stenosis</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>59</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Lt MCA stenosis</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>13</td>
<td>70</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Lt MCA stenosis</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>14</td>
<td>73</td>
<td>F</td>
<td>Minor complete stroke</td>
<td>Rt MCA stenosis</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>15</td>
<td>66</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Lt MCA occlusion</td>
<td>Deep white matter</td>
</tr>
<tr>
<td>16</td>
<td>73</td>
<td>F</td>
<td>TIA</td>
<td>Lt MCA occlusion</td>
<td>None</td>
</tr>
<tr>
<td>17</td>
<td>55</td>
<td>M</td>
<td>Minor complete stroke</td>
<td>Rt MCA occlusion</td>
<td>Lacunar</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
and PW MRI-CBV were determined in each ROI. PET-CVR was calculated as CVR (%) = ([acetazolamide challenge CBF – resting CBF]/resting CBF) × 100.

Statistical Analysis
Data were expressed as the mean ± SD, and differences between physiological variables were examined by repeated-measures analysis of variance. Correlations between various parameters were determined by linear regression analysis. Statistical significance was set at the P < 0.05 level. The accuracy of PW MRI-CBV to detect abnormal reduction of PET-CVR was determined by receiver operating characteristic curves.

Results
Table 2 shows the values of the physiological data measured in all subjects immediately after PW MRI and during PET at rest and with acetazolamide administration. No significant differences were observed in PaCO2, Pao2, blood pH, or mean blood pressure.

A total of 24 ROIs in 12 normal subjects and 34 ROIs in 17 patients were analyzed in each image. Normal values obtained from the 24 ROIs in normal subjects were 9.91 ± 2.7 mL/100 g for PW MRI-CBV and 34.7 ± 9.9% for PET-CVR.

Figure 2 shows the PW MRI-CBV and PET-CVR values in each subject and patient. The fit to the regression line of the values obtained in the subjects was significant (P < 0.0001), with a correlation coefficient of -0.713. An elevated PW MRI-CBV value was defined as higher than the mean ± 2 SD obtained in normal subjects (15.3 mL/100 g). A reduced PET-CVR was defined as lower than the mean ± 2 SD obtained in normal subjects (14.9%).

The PW MRI-CBV and PET-CVR methods obtained identical results in 88.2% of the ROIs: 23.5% (8/34 ROIs) were true positives and 64.7% (22/34) were true negatives (Figure 2). PW MRI-CBV identified false-positives and false-negatives in 5.9% (2/34 ROIs) each. Assuming the PET-CVR as the true determinant of hemodynamic impairment, PW MRI-CBV provided 80.0% sensitivity and 91.7% specificity, with 80.0% positive predictive value and 91.7% negative predictive value for detecting patients with reduced CVR.

Sensitivity and specificity at the cutoff point (15.3 mL/100 g, consistent with the mean ± 2 SD of the CBV in normal subjects) lying closest to the upper corner of the receiver operating characteristic curve were 80.0% and 91.7% for PW MRI-CBV (Figure 3). Representative PET and PW MR images in Case 13 are shown in Figure 4.

Discussion
The present study demonstrated that CBV measurement by PW MRI can indicate hemodynamic impairment without exposure to ionizing radiation.

Recent prospective studies have demonstrated that reduced CVR after acetazolamide administration, defined as lower positives and 64.7% (22/34) were true negatives (Figure 2). PW MRI-CBV identified false-positives and false-negatives in 5.9% (2/34 ROIs) each. Assuming the PET-CVR as the true determinant of hemodynamic impairment, PW MRI-CBV provided 80.0% sensitivity and 91.7% specificity, with 80.0% positive predictive value and 91.7% negative predictive value for detecting patients with reduced CVR.

Sensitivity and specificity at the cutoff point (15.3 mL/100 g, consistent with the mean ± 2 SD of the CBV in normal subjects) lying closest to the upper corner of the receiver operating characteristic curve were 80.0% and 91.7% for PW MRI-CBV (Figure 3). Representative PET and PW MR images in Case 13 are shown in Figure 4.

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Recent prospective studies have demonstrated that reduced CVR after acetazolamide administration, defined as lower

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PW MRI</th>
<th>Rest</th>
<th>ACZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>7.41±0.03</td>
<td>7.39±0.04</td>
<td>7.42±0.05</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>40.2±3.1</td>
<td>41.5±4.3</td>
<td>38.2±3.9</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>92.0±4.0</td>
<td>90.3±3.9</td>
<td>94.2±5.1</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>98.3±8.4</td>
<td>97.6±9.3</td>
<td>99.1±9.1</td>
</tr>
</tbody>
</table>

ACZ indicates acetazolamide; Pao2, arterial carbon dioxide tension; Pao2, arterial oxygen tension.

Figure 2. Comparison of CBV values measured by PW MRI and PET values obtained by PET in 24 ROIs in 12 normal subjects (closed circles) and 34 ROIs in 17 patients (open circles). A significant correlation was observed between these 2 values (r = -0.710, P < 0.0001) in normal subjects. The dashed horizontal line shows the mean – 2 SD of the CVR obtained in normal subjects, and the dashed vertical line shows the mean + 2 SD of the CBV. The plot reveals 4 groups: 8 ROIs with reduced PET-CVR and elevated PW MRI-CBV (true positive), 2 ROIs with only reduced PET-CVR (false-negative), 22 ROIs without reduced PET-CVR or elevated PW MRI-CBV (true negative), and 2 ROIs with only elevated PW MRI-CBV (false-positive).
than the mean −2 SD of the CVR or 95% confidence limits obtained in healthy volunteers, can predict the risk of stroke recurrence in patients with symptomatic major cerebral artery occlusive disease.\textsuperscript{16–18} Furthermore, patients with CVR lower than the mean −2 SD of the CVR obtained in healthy volunteers are at risk for cerebral hyperperfusion after carotid endarterectomy.\textsuperscript{19} We used the same value to indicate hemodynamic impairment.

The correlation between CVR and CBV measured by MRI in humans has received little attention.\textsuperscript{20} There is a significant correlation between CVR measured by single-photon emission–computed tomography and CBV measured by PW MRI in patients with major cerebral artery occlusive disease.\textsuperscript{20} The present study demonstrated a similar significant correlation between CVR measured by PET and CBV measured by PW MRI. Furthermore, we revealed the threshold of PW MRI-CBV to detect the patients with reduced CVR. Assuming the PET-CVR as the true determinant of hemodynamic impairment, PW MRI-CBV provided 80.0% sensitivity and 91.7% specificity for detecting patients with reduced CVR. Thus, the PW MRI-CBV method could be used to identify patients with hemodynamic impairment.

The contrast agents used in PW MRI are nondiffusible tracers, so they do not pass through the blood-brain barrier, unlike diffusible tracers. Therefore, PW MRI is sensitive to the blood component in the arteries and veins.\textsuperscript{21} Moreover, the appropriate parameters in the PW MRI sequence mainly reflect the signal from capillary-sized vessels and suppress the signal from larger vessels.\textsuperscript{22} Therefore, PW MRI is likely to reflect the CBV in the brain tissue.

Quantification of hemodynamic states in PW MRI is enabled by the indicator dilution method with arterial input function.\textsuperscript{10–13,20,23} Thus, the quantitative values of PW MRI are influenced by the arterial input function. The present study included only patients with unilateral ICA or MCA occlusive disease, and the arterial input function was obtained from the contralateral MCA. However, the cerebral hemodynamics are impaired more severely in patients with bilateral major cerebral artery occlusive disease than in those with unilateral major cerebral artery occlusive disease.\textsuperscript{24} Whether CBV can be accurately measured by PW MRI in patients with bilateral major cerebral artery occlusive disease remains unclear. Furthermore, it was reported that CBV was higher with MRI than with PET, which may reflect an underestima-
tion of the arterial input function.

An individual scale factor should be applied to PW MRI measurements to improve the agreement with PET.

Conclusion

The present relatively small study demonstrated that CBV measured by PW MRI can accurately detect hemodynamic impairment in patients with unilateral major cerebral artery occlusive disease. PW MRI involves no exposure to ionizing radiation and requires less than a few minutes of scanning time, so can easily be added to any clinical MRI examination. However, several investigators have recently demonstrated that CBV is not always increased with reductions in cerebral perfusion pressure under clinical circumstance. Thus, further investigation regarding the relationship between the PW MRI-CBV value and the risk of stroke recurrence in patients with symptomatic major cerebral artery occlusive disease or the risk for cerebral hyperperfusion after carotid endarterectomy is necessary.

Acknowledgments

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References

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