Brain Temperature Measured Using Proton MR Spectroscopy Detects Cerebral Hemodynamic Impairment in Patients With Unilateral Chronic Major Cerebral Artery Steno-Occlusive Disease

Comparison With Positron Emission Tomography

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Background and Purpose—Brain temperature is determined by the balance between heat produced by cerebral energy turnover and heat removed by cerebral blood flow. The purpose of the present study was to investigate whether brain temperature measured noninvasively using proton MR spectroscopy can detect cerebral hemodynamic impairment in patients with unilateral chronic internal carotid or middle cerebral artery occlusive disease when compared with positron emission tomography.

Methods—Brain temperature, cerebral blood flow, and metabolism were measured using proton MR spectroscopy and $^{15}$O-positron emission tomography, respectively, in 21 normal subjects and 37 patients. Positron emission tomography images were coregistered with MR images and resliced automatically using image analysis software. Regions of interest placed in both cerebral hemispheres on MR images were automatically superimposed in these resliced positron emission tomography images.

Results—A significant correlation was observed between brain temperature difference (affected hemisphere–contralateral hemisphere) and both cerebral blood volume and oxygen extraction fraction ratio (affected hemisphere/contralateral hemisphere; $r=0.607$; $P=0.0004$ and $r=0.631$; $P=0.0002$). With abnormally elevated cerebral blood volume or oxygen extraction fraction ratio defined as higher than the mean $±$ 2 SDs obtained from normal subjects, brain temperature difference provided 86% or 92% sensitivity and 87% or 84% specificity with 80% or 73% positive and 91% or 95% negative predictive values for detecting abnormally elevated cerebral blood volume or oxygen extraction fraction ratios, respectively.

Conclusions—Brain temperature measured using proton MR spectroscopy can detect cerebral hemodynamic impairment in patients with unilateral chronic major cerebral artery steno-occlusive disease. (Stroke. 2009;40:3012-3016.)

Key Words: brain temperature ■ hemodynamic impairment ■ magnetic resonance spectroscopy ■ positron emission tomography

As cerebral perfusion pressure falls, cerebral blood flow (CBF) is first maintained by dilation of precapillary resistance vessels in a process known as cerebrovascular autoregulation.1,2 Such dilation of vessels also results in increased cerebral blood volume (CBV).3 Increased preoperative CBV in the cerebral hemisphere ipsilateral to carotid endarterectomy represents a significant independent predictor of postoperative cerebral hyperperfusion,4 which may cause intracerebral hemorrhage4 or cognitive impairment5 after surgery.

With more severe reductions in cerebral perfusion pressure, the capacity for compensatory vasodilation is exceeded, autoregulation fails, and CBF begins to decline. A progressive increase in oxygen extraction fraction (OEF) is instead used to maintain cerebral oxygen metabolism and brain function.1 This form of cerebral hemodynamic failure has been termed “misery perfusion.”5 Misery perfusion increases the risk of stroke recurrence in patients with symptomatic major cerebral arterial occlusive disease when medically treated.6 Although CBV can be assessed using perfusion-weighted MR imaging7 or positron emission tomography (PET), OEF can only be measured using PET.

Temperature can be measured noninvasively with MR spectroscopy (MRS).8–11 Experimental studies in phantoms12 and experimental models13 have shown close correlations

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between temperature as measured by MRS and implanted probes. MRS has also been used to measure brain temperature (BT) in healthy adult human volunteers, infants, and patients with brain tumors and acute ischemic stroke.

In the healthy human, BT at rest is determined by the balance between heat produced by cerebral energy turnover, which is identical to cerebral metabolism, and heat that is removed primarily by CBF. We hypothesized that these 2 factors would also affect BT in patients with chronic cerebral ischemia. The present study therefore investigated whether BT measured using proton MRS can detect cerebral hemodynamic impairment in patients with unilateral chronic internal carotid or middle cerebral artery (ICA or MCA, respectively) steno-occlusive disease when compared with PET.

Subjects and Methods

Healthy Volunteers
Volunteers comprised 21 healthy adults (6 women, 15 men) with a mean age of 38 years (range, 20 to 61 years). Subjects with a history of hypertension, diabetes mellitus, atrial fibrillation, or pulmonary disease were excluded. Subjects with leukoaraiosis or asymptomatic lacunar infarction on conventional brain MRI were also excluded.

Patients
This study also included 37 patients (7 women, 30 men) with a mean age of 63 years (range, 44 to 82 years) showing unilateral chronic MCA or ICA steno-occlusive diseases. All patients had experienced cerebral ischemic events. Conventional MRI was performed in all patients with no cortical infarctions observed in any. Seventeen patients had transient ischemic attacks with (8 patients) or without (9 patients) definite cerebral border zone infarction on MRI. The remaining 20 patients experienced minor complete strokes with definite cerebral border zone infarction on MRI. Cerebral angiography with arterial catheterization and/or MR angiography using a 3.0-T imager demonstrated ICA stenosis (stenosis >70%) in 4 patients, ICA occlusion in 18 patients, MCA stenosis (stenosis >50%) in 7 patients, and MCA occlusion in 8 patients. No patients showed occlusion or stenosis of more than 50% in the contralateral ICA or MCA.

All study protocols were approved by the local ethics committee, and written informed consent was obtained from all subjects before enrollment in the study.

Magnetic Resonance Spectroscopy
We used a 3.0-T imager (SIGNA Excite HD; General Electric, Milwaukuee, Wis) with a “birdcage” quadrature head coil. First, all subjects underwent axial short T1 inversion recovery (STIR) imaging. In STIR imaging for each subject, one slice through the centrum semiovale was selected and a single-voxel region of interest (ROI) was manually and symmetrically placed in bilateral cerebral hemispheres (Figure 1). Voxel size was 17×30×15 mm³. Next, acquisition of proton MRS was performed using point-resolved spectroscopy without water decoupling to estimate BTs using the following parameters: repetition time, 2000 ms; echo time, 144 ms; data size, 4 K; spectral width, 5000 Hz; and 96 acquisitions (3.9 minutes).

While obtaining MRS, ambient temperature was maintained at 21°C to 25°C. All patients underwent MRS ≥1 month after the last ischemic event.

Positron Emission Tomography
PET studies were performed using a SET-3000GCT/M scanner (PET/CT; Shimadzu Corp, Kyoto, Japan). This scanner uses gadolinium silica oxide detectors and provides 59 slices with 2.6-mm slice thickness. The axial field of view was 156 mm. Spatial resolution was 3.5-mm full width at half maximum at 1 cm in-plane and 4.2-mm full width at half maximum at center axially. In this study, the scanner was operated in a static scan mode with dual-energy window acquisition for scatter correction. The coincidence time window was set to 10 ns. To reduce the counting rate of random coincidences and scatter coincidences attributable to radioactivity outside the field of view, we used a shield module consisting of 7-mm-thick lead plates attached to the gantry bed and covering the breast and shoulder of the subject.

Before emission scans, a transmission scan (3 minutes) with a 137Cs point source was performed using a bismuth germinate transmission detector ring coaxially attached to the gadolinium silica oxide emission detector ring. CBF was determined while the subject continuously inhaled C15O2 through a mask. Measurements of cerebral metabolic rate of oxygen (CMRO2) and OEF were obtained during continuous inhalation of 15O2. Data were collected for 5 minutes. A single breath of C15O was used to measure CBV. CBV, CMRO2, and OEF were calculated using the steady-state method, and CMRO2 and OEF were corrected by CBV. All patients underwent the PET study after the MRS study with both studies performed on the same day.

Data Analysis
Raw data from proton MRS were transferred to a postprocessing computer (apodization; 1 Hz and fast Fourier transform) analyzed by the automatic curve fitting procedure and decomposed into Lorentzian peak components using our custom-made software. In MRS, a Lorentzian line shape is commonly assumed based on a one-exponential transverse relaxation behavior of the spins. The real part of the signal was thus used to estimate spectral parameters in a line shape fitting analysis. BT for each voxel was calculated from the chemical shift difference between water and N-acetylaspartate signals (δH2O-NAA) using calibration data from Cadet et al: T (°C)=286.9 to 94δ(H2O-NAA).

STIR MR images with ROIs and PET data were transferred to a postprocessing workstation and analyzed using DrView/LINUX image analysis software (Asahi Kasei, Tokyo, Japan). Oblique planes of these 2 methods differed, so PET images were coregistered with STIR MR images. PET images consisting of 59 slices with 2.6-mm thickness were resliced automatically to 22 slices with 4-mm thickness and ROIs on STIR MR images were automatically superimposed in these resliced PET images. These resliced images and ROIs were then generated in the oblique planes and positions identical to the STIR MR images, respect-
Figure 2. CBF and metabolism images obtained using PET in the patient from Figure 1. ROIs are identical to those in Figure 1. Although CBF is more reduced in the right cerebral hemisphere than in the left cerebral hemisphere, no difference in CMRO₂ is apparent between cerebral hemispheres. As a result, CBF and OEF are relatively elevated in the right cerebral hemisphere.

The ratio of the value in the affected hemisphere to that in the contralateral hemisphere was then calculated in each PET-ROI image. The difference between BT in the affected hemisphere and that in the contralateral hemisphere (affected hemisphere–contralateral hemisphere) was also calculated in each STIR MR imaging ROI image and was defined as ΔBT.

The 21 healthy volunteers were assigned to one of 2 groups, each consisting of 11 or 10 subjects who underwent MRS or PET study, respectively. In each group, ΔBT, CBF, CBV, CMRO₂, or OEF ratio was calculated with the left cerebral hemisphere defined as the affected side.

Statistical Analysis

Data are expressed as the mean±SD. Relationships between parameters in patients and those in normal subjects were evaluated using Mann-Whitney U test. Correlations between various parameters were determined using linear and polynomial regression analyses and by computing regression equations and correlation coefficients, and the function of better fit was determined. Statistical significance was set at the P<0.05 level. The accuracy of ΔBT to detect abnormally reduced CBF, elevated CBV, reduced CMRO₂, or elevated OEF ratio was determined by a receiver operating characteristic curve when a correlation between any 2 parameters was significant. Abnormally reduced CBV or CMRO₂ ratios were defined as lower than the mean −2 SD obtained from healthy subjects and abnormally elevated CBV or OEF ratios were defined as higher than the mean +2 SD obtained from healthy subjects. The curve was calculated in increments or decrements of 1 SD from the mean value of ΔBT obtained in healthy subjects.

Results

As shown in the Table, although CBF ratio and CMRO₂ ratio were significantly lower in patients than in normal subjects, CBV ratio and OEF ratio were significantly higher in patients than in normal subjects. However, ΔBT did not differ between the 2 groups.

Although no correlation was identified between OEF ratio and CBF ratio or CMRO₂ ratio, a significant linear correlation between OEF ratio and CBV ratio (R=0.604; P=0.0001) was observed.

Table. Characteristics of Normal Subjects and Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Subjects</th>
<th>Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔBT (°)</td>
<td>−0.01±0.25</td>
<td>0.05±0.70</td>
<td>NS</td>
</tr>
<tr>
<td>CBF ratio</td>
<td>0.99±0.05</td>
<td>0.86±0.11</td>
<td>0.0004</td>
</tr>
<tr>
<td>CBV ratio</td>
<td>1.00±0.05</td>
<td>1.08±0.14</td>
<td>0.0482</td>
</tr>
<tr>
<td>CMRO₂ ratio</td>
<td>1.00±0.04</td>
<td>0.88±0.10</td>
<td>0.0003</td>
</tr>
<tr>
<td>OEF ratio</td>
<td>0.99±0.05</td>
<td>1.06±0.11</td>
<td>0.0482</td>
</tr>
</tbody>
</table>

NS indicates not significant.

Figure 3 shows comparisons of ΔBT and CBF ratio in each patient. No significant fit to any regression line was observed for the obtained values.

Figure 4 shows comparisons of ΔBT and CBV ratio in each patient. The fit to the square regression line of the values was significant (P=0.0004) with a correlation coefficient of 0.607. CBV ratio tended to increase with increasing ΔBT above a critical level of approximately 0°. With abnormally elevated CBV ratio defined as higher than the mean +2 SD obtained in healthy subjects (1.10), sensitivity and specificity for ΔBT in the cutoff point lying closest to the left upper corner of the receiver operating characteristic curve in detecting abnormally elevated CBV ratio were 86% and 87% (cutoff point, 0.24°: mean +1 SD of the control value obtained from healthy subjects), respectively. With this cutoff point, positive and negative predictive values were 80% and 91%, respectively.

Figure 5 shows comparisons of ΔBT and CMRO₂ ratio in each patient. The fit to the linear regression line of the values was significant (P=0.0001) with a correlation coefficient of 0.587. With abnormally reduced CMRO₂ ratio defined as lower than the mean −2 SD obtained in healthy subjects (0.92), sensitivity and specificity for the ΔBT with the cutoff point lying closest to the left upper corner of the receiver operating characteristic curve in detecting abnormally reduced CMRO₂ ratio were 43% and 100% (cutoff point, −0.26°: mean −1 SD of control value obtained from healthy subjects), respectively. For this cutoff point, positive and negative predictive values were 100% and 52%, respectively.

Figure 6 shows comparisons of ΔBT and OEF ratio in each patient. The fit to the square regression line of the values was significant (P=0.0002) with a correlation coefficient of 0.631. OEF ratio tended to increase with increasing ΔBT above a critical level of approximately 0°. With an abnormally elevated
OEF ratio defined as higher than the mean +2 SD obtained from healthy subjects (1.09), sensitivity and specificity for ΔBT with the cutoff point lying closest to the left upper corner of the receiver operating characteristic curve in detecting abnormally elevated OEF ratio were 92% and 84% (cutoff point, 0.24°; mean +1 SD of the control value obtained from healthy subjects), respectively. With this cutoff point, positive and negative predictive values were 73% and 95%, respectively.

Discussion

In healthy humans, BT is determined by the balance between heat produced by cerebral energy turnover and the heat removed by CBF.14 Our data regarding the significant correlation between ΔBT and OEF ratio and the increase in OEF ratio with increasing ΔBT above a critical level of approximately 0° suggest that the balance between cerebral perfusion and cerebral metabolism determines BT in chronically ischemic human brain, and cerebral perfusion reduced relative to cerebral metabolism causes decreased removal of heat produced by cerebral energy turnover, resulting in increased BT.

The present study showed a significant correlation between ΔBT and CBV ratio. In the ischemic brain with increased OEF, precapillary resistance vessels dilate maximally against severe reductions in cerebral perfusion pressure, resulting in increased CBV.1,2,5 Actually, the present study demonstrated a positive correlation between CBV ratio and OEF ratio, supporting previous findings.18 A correlation between ΔBT and CBV ratio may thus reflect a correlation between ΔBT and OEF ratio.

The present study also showed a significant correlation between ΔBT and CMRO₂ ratio. In particular, specificity and positive predictive value for ΔBT in detecting an abnormally reduced CMRO₂ ratio were 100%. All patients with ΔBT <−0.26° exhibited an abnormally reduced CMRO₂ ratio. A negative ΔBT theoretically implies reduction of heat produced by cerebral energy turnover, suggesting a reduction in cerebral metabolism in the affected cerebral hemisphere. Our data support this theory.

In chronic cerebral ischemia, reduced CBF includes 2 pathophysiologically different conditions: misery perfusion due to hemodynamic compromise and matched hypometabolism due to incomplete infarction.19 BT is theoretically increased in the former condition and decreased in the latter condition. This may be why no significant correlation was seen between ΔBT and CBF ratio.

In the present study, ΔBT provided high sensitivity and specificity with high positive and negative predictive values for detecting abnormally elevated CBV or OEF ratio. An abnormally elevated CBV or OEF ratio was defined as >1.10 or 1.09, respectively. Fukuda et al measured CBV using perfusion-weighted MRI in patients with unilateral cervical carotid stenosis and categorized patients with a CBV ratio >1.1 as having hemodynamic impairment.3 Such patients are reportedly at high risk for cerebral hyperperfusion after...
carotid endarterectomy. Grubb et al also categorized patients with an OEF ratio >1.082 as having misery perfusion and reported that such patients are at high risk for subsequent stroke among patients with symptomatic ICA occlusive disease when treated medically. Because the cutoff point for CBV or OEF ratio is approximately identical to that used in the present study, our results suggest that ΔBT may identify patients at high risk for cerebral hyperperfusion after carotid endarterectomy or stroke recurrence.

The present study possesses several limitations that require discussion. First, the cerebral hemisphere with symptomatic hemodynamic impairment often exhibits brain atrophy. In that situation, the proportion of cerebrospinal fluid occupying the ROI for measurement of BT is high. Cerebrospinal fluid in the ROI may reduce the accuracy of brain tissue temperature measured by MRS. Second, the present study included only patients with unilateral ICA or MCA occlusive disease and used the difference in BT as compared with the unaffected side to detect hemodynamic impairment in the affected cerebral hemisphere. However, hemodynamic cerebral ischemia is more severe in patients with bilateral major cerebral artery occlusive disease than in those with unilateral major cerebral artery occlusive disease. BT is affected by body temperature, but not by ambient temperature. Thus, whether cerebral hemodynamic impairment in patients with bilateral major cerebral artery occlusive disease can be detected using the absolute BT remains unclear. Third, a single-voxel ROI for measurement of BT was placed on the slice through the centrum semiovale. Although a topographical map of brain temperature can be obtained by using a multivoxel method,13 BT values acquired from a single voxel may provide more accurate MRS estimation of brain tissue temperature than those acquired from multiple voxels. Finally, normal values were obtained from healthy subjects who were younger than the patients. However, unaffected side difference and affected-to-contralateral side asymmetry were used to determine relative BT, CBF, and metabolism in the affected cerebral hemisphere. Differences in age may thus have minimally affected the present results.

Conclusions

The present study demonstrated that BT measured using proton MRS can detect cerebral hemodynamic impairment in patients with unilateral chronic major cerebral artery steno-occlusive disease. Further investigations regarding the relationships between BT and risk of cerebral hyperperfusion after carotid endarterectomy or stroke recurrence in patients with symptomatic major cerebral artery occlusive disease would be of benefit.

Disclosures

None.

References

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