Abnormal Intravoxel Cerebral Blood Flow Heterogeneity in Human Ischemic Stroke Determined by Dynamic Susceptibility Contrast Magnetic Resonance Imaging

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Background and Purpose—The determination of cerebral blood flow heterogeneity (FH) by dynamic susceptibility contrast (DSC) magnetic resonance imaging has recently been proposed as a tool to predict final infarct size in acute stroke. In this study, we describe the evolution of FH during the first week as well as its correlation to the patients’ clinical status.

Methods—Ten patients with ischemic stroke were studied with DSC MRI and diffusion-weighted imaging in hyperacute (<6 hours) phase, at 24 hours, and 1 week after symptom onset. In addition to intravoxel FH, cerebral blood volume (CBV), cerebral blood flow (CBF), and contrast agent mean transit time (MTT) were determined from DSC MRI. All patients were evaluated neurologically with National Institute of Health Stroke Scale concurrently with the imaging sessions.

Results—All patients showed infarct growth, judged by diffusion-weighted imaging, during the week with simultaneous decrease in the sizes of FH, CBV, CBF, and MTT abnormalities. The FH abnormality was shown to be larger than CBV and CBF abnormalities at the hyperacute phase and 24 hours, but smaller than MTT abnormality in all 3 imaging sessions. The sizes of hyperacute FH, CBV, CBF, and MTT abnormalities correlated well with infarct size at 24 hours and at 1 week. Additionally, FH was the only perfusion parameter that correlated with the clinical score.

Conclusions—FH predicts infarct size equally well with the other perfusion parameters but is superior in correlation with the clinical score. FH can easily be incorporated to hyperacute stroke imaging without additional efforts. (Stroke. 2005; 36:44-49.)

Key Words: magnetic resonance imaging ■ perfusion ■ stroke

Rapid evaluation of patients with hyperacute ischemic stroke is of great importance as application of recombinant tissue plasminogen activator improves outcome only when used within hours of symptom onset.1,2 Dynamic susceptibility contrast (DSC)3 magnetic resonance imaging (MRI), assessing hypoperfused brain regions, and diffusion-weighted MRI (DWI), detecting tissue with ischemic damage,4 are increasingly used for this purpose. DSC MRI has been used for creating parametric maps of cerebral blood volume (CBV),5 cerebral blood flow (CBF),6,7 and contrast agent mean transit time (MTT),8 which all have been widely used to assess stroke evolution.9–13 DSC MRI has also been demonstrated to be able to assess intravoxel distribution of CBF and flow heterogeneity (FH),14,15 but it has not been widely used.

The CBF in normal human capillaries is inherently widely distributed around a mean flow,16,17 with a portion of blood cells flowing too fast for the oxygen molecules to be efficiently extracted into tissue. Although in normal human brain, the mean CBF differs considerably among various regions,18 the intravoxel FH is not spatially dependent.14 However, in cases of lowered local cerebral perfusion pressure, as in ischemic stroke, there is a significant reduction in the high-flow components, which improves oxygen delivery to the tissue15,16 and is manifested as a less dispersed CBF distribution.17,19 The assessment of FH may therefore be an important indicator of the state of tissue vasoregulatory control mechanism and could provide important insight of the state and development of ischemic stroke.
TABLE 1. Patient Data

<table>
<thead>
<tr>
<th>Patient/Sex/Age/Paretic Side/TOAST</th>
<th>MRI Since Stroke Onset (h) 1 2 3</th>
<th>NIHSS 1 2 3</th>
<th>DWI1</th>
<th>DWI2</th>
<th>DWI3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/78/L/5</td>
<td>3.5</td>
<td>30.0</td>
<td>144</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>2/M/51/L/5</td>
<td>4.9</td>
<td>23.8</td>
<td>191</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>3/F/74/R/2</td>
<td>5.5</td>
<td>26.2</td>
<td>153</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>4/F/72/R/5</td>
<td>4.8</td>
<td>28.3</td>
<td>147</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>5/M/88/L/2</td>
<td>2.7</td>
<td>24.5</td>
<td>171</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>6/M/59/R/2</td>
<td>5.7</td>
<td>29.7</td>
<td>139</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>7/M/78/L/5</td>
<td>3.8</td>
<td>30.6</td>
<td>169</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>8/M/48/R/2</td>
<td>3.8</td>
<td>24.8</td>
<td>164</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>9/F/87/L/5</td>
<td>5.0</td>
<td>31.0</td>
<td>175</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>10/F/67/L/2</td>
<td>3.5</td>
<td>29.5</td>
<td>174</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mean</td>
<td>4.3</td>
<td>27.8</td>
<td>163</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

Patient number, gender, age, the affected hemisphere, and TOAST classification22 are presented for each patient.

The time of imaging after the onset of symptoms, NIHSS, and the size of diffusion lesion indicating infarct size are presented for all 3 imaging sessions: the hyperacute phase (1), 24 hours (2), and 1 week (3).

M indicates male; F, female; L, left; R, right; TOAST; Trial of Org 10172 in Acute Stroke Treatment.

The purpose of the present study was to follow the course of the size of the FH abnormality during the first week of ischemic stroke and compare it with the corresponding courses of CBV, CBF, and MTT abnormalities. Furthermore, the correlation between the sizes of FH, CBV, CBF, and MTT abnormalities with the final infarct size, determined by DWI, and clinical score was examined.

MATERIALS AND METHODS

Patients

Patient data are presented in Table 1. Ten patients with ischemic stroke were prospectively studied with MRI and neurological evaluation with National Institutes of Health Stroke Scale (NIHSS) in hyperacute phase (<6 hours), at 24 hours, and at 1 week after symptom onset. The inclusion criteria were: (1) admission of the patient with an acute hemiparesis within 4 hours of symptom onset to the emergency room and initiation of MRI within 6 hours of symptom onset; (2) NIHSS ≥5; (3) conscious state; and (4) first-ever stroke. Patients not fulfilling any of these criteria were excluded. None of the patients was treated with thrombolytic therapy or experimental neuroprotective agents. The study protocol was approved by the ethical committees of Departments of Radiology and Neurology at Helsinki University Central Hospital and informed consent was obtained from each patient or patient’s relative before the study.

MRI

MR examinations were performed with a 1.5-T scanner (Magnetom Vision; Siemens Medical Systems). DWI was performed with a fat-suppressed spin-echo planar imaging sequence (TR/TE=4000/103) covering 19 5-mm-thick slices (interslice gap 1.5 mm; field of view 260 mm; matrix size 96×128 interpolated to 256×256) in 3 orthogonal directions with a b-value 1000 s/mm². In addition, a T2-weighted reference image (b=0) was obtained for the calculation of apparent diffusion coefficient. DSC MRI was performed with a fat-suppressed spin-echo planar imaging sequence (TR/TE=1500/78) covering 7 5-mm-thick slices (interslice gap 1.5 mm; field of view 260 mm; matrix size 116×256 interpolated to 256×256 [8 patients] or 96×128 interpolated to 128×128 [2 patients]), which were set to cover the DWI-based ischemic lesion and imaged repeatedly 40 times with, after the collection of 7 baseline images, gadopentetate dimeglumine (Magnevist; Schering AG; 0.2 mmol/kg body weight) injected into the antecubital vein, immediately followed by an 8-ml bolus of saline at a speed of 5 mL/s using an MR-compatible power injector (Spectris; Medrad).

Diffusion Images

A direction-independent approximation of the diffusion was calculated as the average of the 3 DW images. The apparent diffusion coefficient was calculated with a commercially available software program (MatLab, Mathworks; The Mathsoft Inc) as the average of the slopes between the natural logarithms of the T2-weighted reference image and the DW image in each diffusional direction.

Perfusion Images

Tissue and arterial concentration levels were determined assuming a linear relationship between intravascular concentration of gadopentetate dimeglumine and transverse relaxation rate. CBV was calculated in each voxel as the area under the first pass of the tissue concentration time curve using global integration constraints. The shape of the arterial input function was determined at the nonischemic hemisphere from 3 to 4 pixels located within small branches of the middle cerebral artery. The tissue impulse response was obtained by deconvolving the tissue concentration time curve with the arterial input function in each voxel. CBV was subsequently determined as the height of the tissue impulse response⁶ and MTT as the ratio CBV:CBF.⁶

The distribution of transit times was determined in each voxel as the negative slope of the tissue impulse response and transformed into a probability density function of relative flow rates (FH), assuming intravoxel capillary pathways of equal length.¹⁴ The FH in each voxel was subsequently compared with a reference distribution describing normal tissue FH,¹⁴ and the significance of similarity was quantified by the Kolmogorov-Smirnov test.¹⁴ The FH was judged abnormal if it deviated from reference FH statistically significantly (P<0.05), denoted as FH(05), and statistically very significantly (P<0.01), denoted as FH(01).

Region of Interest Analysis

Infarcted tissue was determined as the region of visually judged decreased diffusion in the average diffusion image and to eliminate the effect of T2 shine-through by reviewing the area in the apparent diffusion coefficient image. The hypoperfused tissue was determined in FH, CBV, CBF, and MTT maps as the region that appeared visually abnormal compared with the corresponding contralateral region. The size of the ischemic lesion and the perfusion abnormality were determined by multiplying the corresponding area by the slice thickness and assuming the interslice gap to contain a lesion or an abnormality of the same surface area as the slice above it. All the regions of interest were manually drawn by a single observer (J.P.), and the analysis was performed with commercially available image analysis software (Alice; Perceptive Systems, Inc, Boulder, Col).
TABLE 2. The Sizes of Perfusion Abnormalities (CBV, CBF, MTT, and FH) Are Presented for All 3 Imaging Sessions

<table>
<thead>
<tr>
<th>Patient</th>
<th>CBV1</th>
<th>CBF1</th>
<th>FH1(01)</th>
<th>FH1(05)</th>
<th>MTT1</th>
<th>CBV2</th>
<th>CBF2</th>
<th>FH2(01)</th>
<th>FH2(05)</th>
<th>MTT2</th>
<th>CBV3</th>
<th>CBF3</th>
<th>FH3(01)</th>
<th>FH3(05)</th>
<th>MTT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>4.9</td>
<td>4.3</td>
<td>5.2</td>
<td>11.5</td>
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<td>2.1</td>
<td>3.2</td>
<td>5.9</td>
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<td>0.2</td>
<td>0.2</td>
<td>0.5</td>
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</tr>
<tr>
<td>2</td>
<td>14.4</td>
<td>14.9</td>
<td>10.6</td>
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<td>12.8</td>
<td>46.0</td>
<td>2.1</td>
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<td>0.4</td>
<td>0.5</td>
<td>14.6</td>
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<tr>
<td>3</td>
<td>44.8</td>
<td>46.6</td>
<td>20.3</td>
<td>47.4</td>
<td>81.9</td>
<td>15.1</td>
<td>19.2</td>
<td>14.9</td>
<td>20.0</td>
<td>29.1</td>
<td>6.5</td>
<td>7.4</td>
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<td>4.2</td>
<td>14.7</td>
<td>62.3</td>
<td>73.2</td>
<td>85.3</td>
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<td>85.0</td>
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<td>0.5</td>
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<td>3.7</td>
<td>5.5</td>
<td>6.7</td>
<td>7.3</td>
<td>1.4</td>
<td>1.9</td>
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<td>3.9</td>
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<td>1.2</td>
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<td>16.0</td>
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<td>51.7</td>
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<td>10.2</td>
<td>20.8</td>
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<tr>
<td>7</td>
<td>3.3</td>
<td>6.3</td>
<td>0.0</td>
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<td>0.0</td>
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<td>8</td>
<td>10.9</td>
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<td>2.8</td>
<td>6.0</td>
<td>5.9</td>
<td>7.3</td>
<td>11.6</td>
<td>1.3</td>
<td>2.8</td>
<td>1.2</td>
<td>1.8</td>
<td>5.1</td>
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<td>9</td>
<td>7.0</td>
<td>8.7</td>
<td>86.5</td>
<td>101.7</td>
<td>148.9</td>
<td>6.4</td>
<td>7.3</td>
<td>24.1</td>
<td>57.8</td>
<td>127.5</td>
<td>2.3</td>
<td>3.9</td>
<td>29.7</td>
<td>37.3</td>
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<tr>
<td>10</td>
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<td>86.4</td>
<td>112.8</td>
<td>121.0</td>
<td>131.5</td>
<td>14.0</td>
<td>45.3</td>
<td>87.6</td>
<td>91.6</td>
<td>115.8</td>
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<td>8.4</td>
<td>6.0</td>
<td>6.1</td>
<td>35.9</td>
</tr>
<tr>
<td>Mean</td>
<td>18.2</td>
<td>22.1</td>
<td>34.5</td>
<td>43.2</td>
<td>61.2</td>
<td>6.6</td>
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<td>2.5</td>
<td>4.0</td>
<td>6.4</td>
<td>8.0</td>
<td>16.3</td>
</tr>
</tbody>
</table>

1 indicates the hyperacute phase; 2, 24 hours; 3, 1 week.

Statistical Analyses

The Spearman correlation coefficient was used to calculate the correlation of the sizes of hyperacute FH, CBV, CBF, and MTT abnormalities with ischemic lesion size and NIHSS. Wilcoxon matched-pairs signed-rank test was used to assess the significance of the difference of the sizes of the perfusion abnormalities in each imaging session and the temporal changes in the size of each abnormality. Statistical analyses were performed with a statistical software package (SPSS Win 11.0; SPSS Inc), and in all cases a 2-tailed $P<0.05$ was considered statistically significant.

Results

The sizes of ischemic lesions and perfusion abnormalities are presented for all 10 patients in Tables 1 and 2, and the differences of the lesion sizes are in Table 3. A typical case is presented in the Figure. All 10 patients showed growth in the ischemic lesion size during the week, with the size of the diffusion lesion increasing from the hyperacute phase to 24 hours ($P<0.01$) and further from 24 hours to 1 week ($P<0.01$). Simultaneously, the sizes of all the perfusion abnormalities decreased from the hyperacute phase to 24 hours ($P<0.01$ for CBV, CBF, and FH(05); $P<0.05$ for FH(01) and MTT) and further from 24 hours to 1 week ($P<0.01$ for CBV, CBF, FH(05), and MTT; $P<0.05$ for FH(05)).

Discussion

Despite its high potential in stroke characterization, intravoxel FH has been used only in a few studies. This is the first study to our knowledge to report FH in comparison with CBV, CBF, and MTT in characterizing the evolution of ischemic stroke.

The findings of the present study tally with earlier results in showing that an untreated ischemic lesion increases in size during the first week after the insult, with the increase

TABLE 3. The Differences in the Sizes of DWI-Based Lesion and Perfusion Abnormalities at the Hyperacute Phase, at 24 Hours, and at 1 Week by Nonparametric Wilcoxon Matched-Pairs Signed-Rank Test

<table>
<thead>
<tr>
<th>DWI</th>
<th>Hyperacute</th>
<th>MTT</th>
<th>FH(05)</th>
<th>FH(01)</th>
<th>CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>&lt;MTT†</td>
<td>&gt;FH(05)†</td>
<td>&gt;FH(01)†</td>
<td>&gt;FH(01)†</td>
<td></td>
</tr>
<tr>
<td>&lt;FH(05)†</td>
<td>&gt;FH(01)†</td>
<td>&gt;FH(01)†</td>
<td></td>
<td></td>
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<tr>
<td>&lt;FH(01)*</td>
<td>&gt;CBF†</td>
<td>&gt;CBF*</td>
<td>&gt;CBF</td>
<td>(P=0.45)</td>
<td></td>
</tr>
<tr>
<td>&lt;CBV*</td>
<td>&gt;CBV†</td>
<td>&gt;CBV*</td>
<td>&gt;CBV</td>
<td>(P=0.24)</td>
<td>&gt;CBV†</td>
</tr>
<tr>
<td>24 Hours</td>
<td>&lt;MTT*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;FH(05) (P=0.20)</td>
<td>&gt;FH(05)†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;FH(01) (P=0.58)</td>
<td>&gt;FH(01)†</td>
<td>&gt;FH(01)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;CBF (P=0.65)</td>
<td>&gt;CBF†</td>
<td>&gt;CBF*</td>
<td>&gt;CBF</td>
<td>(P=0.39)</td>
<td></td>
</tr>
<tr>
<td>&gt;CBV (P=0.11)</td>
<td>&gt;CBV†</td>
<td>&gt;CBV*</td>
<td>&gt;CBV</td>
<td>(P=0.24)</td>
<td>&gt;CBV†</td>
</tr>
<tr>
<td>1 Week</td>
<td>&lt;MTT (P=0.72)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;FH(05)*</td>
<td>&gt;FH(05)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;FH(01)*</td>
<td>&gt;FH(01)†</td>
<td>&gt;FH(01)†</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;CBF†</td>
<td>&gt;CBF†</td>
<td>&gt;CBF</td>
<td>(P=0.58)</td>
<td>&gt;CBF</td>
<td>(P=0.39)</td>
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<tr>
<td>&gt;CBV†</td>
<td>&gt;CBV†</td>
<td>&gt;CBV</td>
<td>(P=0.14)</td>
<td>&gt;CBV</td>
<td>(P=0.72)</td>
</tr>
</tbody>
</table>

< and > denote the difference in the volume between the parameter in the heading of the column and the parameter in the row.

The corresponding $P$ values are presented as statistically significant correlation (*$P<0.05$) and very statistically significant correlation (†$P<0.01$).
being more pronounced in the early stages. Also, in line with previous reports, the size of the initial perfusion abnormality exceeded the size of ischemic lesion, with the CBV showing the smallest and the MTT the largest perfusion abnormality.

The discrimination of normal and abnormal FH is based on a threshold for the significance of the difference between the voxel-based FH and the reference FH. Whereas in previous studies using the Kolmogorov–Smirnov test, voxels with $P<0.01$ have been categorized as abnormal, in the present study, the threshold $P<0.05$ was used also. As expected, FH(05) was found to show larger abnormality than FH(01). However, the differences in the sizes were not large, suggesting that the loss of flow heterogeneity, associated with the increased metabolic needs of a tissue, is quite substantial if present. At the hyperacute stage, the sizes of both FH(01) and FH(05) abnormalities correlated equally well to the size of the ischemic lesion on DW images at 1 week, as well as to the clinical scale at all time points, suggesting both methods to be applicable to clinical use. However, the size of hyperacute FH(01) abnormality did not differ significantly from the final ischemic lesion size, whereas the FH(05) did, indicating a possible benefit for using the FH(01) in predicting final ischemic lesion size.

The size of FH(05) abnormality was found to exceed CBV and CBF abnormalities in the hyperacute phase and at 24 hours, suggesting that FH has a regulatory role in tissue hemodynamics as the intravoxel flow distribution is altered in voxels in which the mean flow or capillary volume are not yet compromised. We found no significant difference between

The development of the ischemic lesion and the perfusion abnormalities in a 67-year-old woman (patient 10) during the first week of ischemic stroke. The abnormalities on flow heterogeneity (FH) maps [FH(01) and FH(05)] are presented as color-coded overlays of the voxel-based probability value onto the corresponding CBF map. The ischemic lesion on diffusion-weighted images increases from the hyperacute phase to 24 hours, and further to 1 week, with simultaneous decrease in the sizes of the perfusion abnormalities on FH01, FH05, CBV, CBF, and MTT maps. At the hyperacute phase and at 24 hours, the size of the FH abnormality [both FH(01) and FH(05)] exceeds that of CBV and CBF, but no difference is observed at 1 week. The size of the FH [both FH(01) and FH(05)] abnormality remains smaller than MTT during the whole week.

Perkio et al Abnormal Flow Heterogeneity in Ischemic Stroke
the sizes of CBV, CBF, and FH(05) [nor FH(01)] abnormalities at 1 week after symptom onset. This suggests that the regulatory mechanism operates mainly in acute and early subacute phases of the compromised microcirculation—at 1 week the voxels with initially abnormal FH have either restored normal flow distribution, including the high-flow components, or developed irreversible pathology evident also in the mean flow and capillary volume. Further, the size of the abnormality on the MTT map exceeded the sizes of both the FH(05) and FH(01) abnormalities, indicating that FH is not the most sensitive marker of abnormal microcirculation because MTT can be prolonged without any apparent change in the intravoxel flow distribution.

In line with earlier studies, the sizes of the hyperacute FH, CBV, CBF, and MTT abnormalities were found to correlate with the size of the ischemic lesion at 24 hours and at 1 week. The results of the present study also tally with earlier findings, which reported the initial CBV to most accurately predict the size of the final ischemic lesion. Further, the results confirm the earlier finding that the size of the hyperacute FH(01) abnormality is a more accurate predictor of final ischemic lesion size than the size of hyperacute MTT abnormality, because FH(01) was found to correlate with the final ischemic lesion size better \((P=0.019)\) than MTT \((P=0.043)\). In the present study, the size of hyperacute FH(05) abnormality was also found to correlate with the final ischemic lesion size better \((P=0.022)\) than MTT, underlying the power of FH to assess the endangered voxels more accurately than MTT in the hyperacute phase.

Finally, the results of the present study indicate that the size of the FH abnormality is superior to the sizes of CBV, CBF, and MTT abnormalities in indicating and predicting the clinical manifestation of ischemic stroke. Although the number of patients analyzed in the present study is quite small, the strong correlation of both hyperacute FH(01) and FH(05) with the final ischemic lesion size and NIHSS at 1 week suggests that FH may be a promising marker of the evolution of the clinical status already at the hyperacute phase.

In the present study, the course of development of the sizes of FH, CBV, CBF, and MTT abnormalities were followed during the first week of an untreated ischemic stroke beginning already at the hyperacute phase. All the perfusion abnormalities were found to decrease in size during the first week. In the hyperacute phase and at 24 hours, the FH abnormality was shown to be larger than CBV and CBF abnormalities, whereas no difference was observed at 1 week. In all 3 imaging sessions, MTT was the largest perfusion abnormality. FH was shown to outperform CBV, CBF, and MTT in predicting clinical condition. In accordance with previous studies, the sizes of hyperacute FH, CBV, CBF, and MTT abnormalities were found to correlate with ischemic lesion size at 24 hours and at 1 week. The results of the present study indicate that FH provides information about developing ischemic stroke comparable with other perfusion parameters but is superior in predicting clinical scale.

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