Blood Oxygen Level–Dependent MRI Allows Metabolic Description of Tissue at Risk in Acute Stroke Patients

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Background and Purpose—The delineation of the “penumbra” is of particular interest in acute stroke imaging. The “mismatch concept” applying perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) appears to be an oversimplification of the underlying electrophysiological tissue status. An additional parameter reflecting the metabolic state of the threatened brain tissue would improve our ability to describe the penumbra. One candidate is deoxyhemoglobin (deoxy-Hb) as an indicator of the oxygen extraction fraction that can be visualized by T2*-based blood oxygen level–dependent (BOLD) imaging.

Methods—We analyzed data from 32 patients with acute stroke in the territory of the middle cerebral artery. MRI included fluid-attenuated inversion recovery, DWI, PWI, time-of-flight angiography, and quantitative T2 and T2* (qT2, qT2*) imaging. Follow-up was performed on day 1 and days 5 to 8. We calculated 1/T2' = 1/qT2* - 1/qT2. Changes of T2', representing the deoxy-Hb effect, were analyzed by 3D regions of interest (ROIs): apparent diffusion coefficient lesion day 0 (L0), time-to-peak–lesion day 0 (T0), final infarct size days 5 to 8 (F5–8), lesion growth (LG; F5–8–L0), and surviving tissue (ST; T0–F5–8).

Results—We observed a clear decrease of T2' in the infarcted hemisphere compared with the unaffected control ROIs. The mean value showed the most pronounced loss of T2' signal intensity in L0 (−15.7%), followed by LG (−10.5%) and ST (−8.0%).

Conclusions—The implementation of BOLD imaging in acute stroke MRI offers a noninvasive estimation of the O2 utilization and is able to add additional information concerning the present metabolic state of the threatened brain tissue. The changes in T2' intensity are visually noticeable in the reconstructed T2' images and provide a better estimation of the real penumbra. (Stroke. 2006;37:1778-1784.)

Key Words: penumbra ■ stroke, acute

In acute ischemic stroke, the “penumbra” is defined as brain tissue with loss of electric activity but potential recovery after recanalization of the occluded artery.1,2 The only approved therapy for acute stroke is thrombolytic therapy,3,4 which is believed to save penumbral brain tissue by early recanalization. However, some patients may not present with a relevant penumbra and thrombolysis might not only be nonbeneficial but even dangerous because of its intrinsic risk of intracranial hemorrhage. For this reason, delineation of the ischemic penumbra is of particular interest in acute stroke imaging.

The “mismatch concept” has been suggested to provide an estimate of the real ischemic penumbra and is used in MRI stroke centers within the first 6 hours after stroke onset to select patients who might benefit from thrombolysis.5 Recent findings indicate that the subtraction of the ischemic lesion on diffusion-weighted imaging (DWI) from the blood flow abnormality on perfusion-weighted imaging (PWI) is only a weak approximation of the penumbra;6 PWI cannot reliably discriminate between benign oligemia and penumbra,7 and DWI lesions do not indicate the irreversibly damaged core of infarction because normalization may occur.8 Therefore, an additional parameter reflecting the metabolic state of the threatened brain tissue would improve our ability to describe the penumbra. One candidate is deoxyhemoglobin (deoxy-Hb) in the cerebral capillaries and veins as an indicator of the oxygen extraction fraction (OEF), which can be visualized by T2*-based blood oxygen level–dependent (BOLD) imaging.9 The OEF is significantly increased in the penumbra.10 Therefore, we hypothesized that a signal loss in BOLD imaging should indicate increased OEF and deoxy-Hb in the real penumbra. The present study is, as far as we know, the first one applying T2*-based BOLD imaging to a larger group of patients in an acute stroke situation, combined with a quantitative region of interest (ROI)–based data analysis. In
the future, MRI BOLD imaging may provide a selection criterion for acute stroke treatment according to the individual metabolic state of the brain tissue, rather than sticking to a strict 3- or 6-hour time frame or the less reliable PWI–DWI mismatch estimation.

**Patients and Methods**

We analyzed data from 32 patients (19 males and 13 females) with acute stroke in the territory of the middle cerebral artery (MCA). The mean age was 64.9 ± 13.5 years (mean ± SD), with a range of 35 to 84 years. Immediately after clinical evaluation, acute stroke MRI was performed on a 1.5-T whole body scanner (Magnetom Sonata; Siemens) within the first 6 hours after symptom onset (2.6 ± 1.2 hours), including fluid-attenuated inversion recovery (FLAIR), DWI (apparent diffusion coefficient [ADC]), and PWI (time-to-peak [TTP]), time-of-flight (TOF) angiography, as well as quantitative T2 and T2* imaging (qT2, qT2*). The imaging parameters for the standard sequences including ADC and TTP have been published by Fiehler et al.11

For calculation of the final T2′ BOLD images, qT2 and qT2* data were used. In case of T2, a triple turbo-spin echo sequence with 20 slices was applied (repetition time [TR]=2720 ms; echo time [TE]=14/70/126 ms; flip-angle=150°; field of view=230 mm; matrix=128×128; slice thickness=5 mm; slice spacing=1.5 mm). The corresponding T2′ sequence was an echo-planar triple-echo sequence provided by O.S. with the same spatial resolution but slightly different parameters (TR=3000 ms; TE=24/56/93 ms; flip-angle=24°). The qT2 images were calculated using the MRVision software (Version 1.5.8; MRVision) and formula: $SI(t) = S_0 e^{-t/T2}$. In an analogous manner, qT2′ was computed from the T2′ triple-echo sequence. qT2 is linked to qT2*,12 resulting in T2*-based BOLD images, qT2 and qT2* data with the same spatial resolution but slightly different parameters (TR=3000 ms; TE=24/56/93 ms; flip-angle=24°). The qT2 images were calculated using the MRVision software (Version 1.5.8; MRVision) and formula: $SI(t) = S_0 e^{-t/T2}$. Acquisition time for MRI was <20 minutes in all cases. Except for one case, all patients were treated by systemic thrombolysis using tissue plasminogen activator immediately after acute stroke MRI (<10 minutes). Thrombolysis was indicated by time from symptom onset (maximum 6 hours), evidence of vessel occlusion, size of the infarcted area (<50% of the territory of the MCA), mismatch information, and absence of contraindications.13 Follow-up imaging was performed with each patient on day 1 to verify reperfusion and on days 5 to 8 to define the finally infarcted brain tissue.

A complete data set of an individual patient consisted of the ADC, TTP, and T2′ images of day 0, a TOF angiography of day 0 and day 1 (failed in 3 patients), as well as a FLAIR image of days 5 to 8 (F5–8). All acquired sequences were normalized to a standardized 3D space to assure an optimal 3D comparability between the modalities. For this purpose, a coregistration of all sequences to the qT2 image using the SPM2 software package (Version SPM2b; Wellcome Department of Imaging Neuroscience, University College, London, UK) was followed by a normalization of the qT2 image to the SPM-implemented T2 template. The transformation parameters were consecutively applied to the remainder image data. We used the standard normalization options of SPM and set the voxel size 2×2×2 mm horizontally and 3.5 mm vertically. Changes of T2′, representing the deoxy-Hb effect, were analyzed by 3D ROIs using the MRCro software (Version 1.37; University of Nottingham, Department of Psychology, United Kingdom). The ADC lesion on day 0 was used to define the ischemic core (lesion

### ROI Statistics

<table>
<thead>
<tr>
<th>A. ROI</th>
<th>T2′ Lesion [ms]</th>
<th>T2′ Control [ms]</th>
<th>ΔT2′</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC lesion (L0)</td>
<td>126 ± 34.9</td>
<td>150 ± 40.6</td>
<td>−15.7%</td>
<td>2.38E-05</td>
</tr>
<tr>
<td>LG</td>
<td>132 ± 33.2</td>
<td>148 ± 36.9</td>
<td>−10.5%</td>
<td>1.29E-03</td>
</tr>
<tr>
<td>ST</td>
<td>120 ± 29.2</td>
<td>130 ± 29.4</td>
<td>−8.0%</td>
<td>5.40E-03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Occlusion Type</th>
<th>n</th>
<th>Thrombolysis (t-PA)</th>
<th>TOF (d1) TIMI 3</th>
<th>TOF (d1) TIMI 2</th>
<th>TOF (d1) TIMI 1</th>
<th>TOF (d1) TIMI 0</th>
<th>TOF (d1) Not Available</th>
<th>L0 [cm³]</th>
<th>T0 [cm³]</th>
<th>F5–8 [cm³]</th>
<th>LG [cm³]</th>
<th>ST [cm³]</th>
<th>q=T0/F5–8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid T</td>
<td>6</td>
<td>5 (83%)</td>
<td>0 (0%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
<td>3 (50%)</td>
<td>1 (17%)</td>
<td>13</td>
<td>249</td>
<td>125</td>
<td>121</td>
<td>113</td>
<td>1.71</td>
</tr>
<tr>
<td>MCA trunc + MCA trifurcation</td>
<td>15</td>
<td>15 (100%)</td>
<td>8 (53%)</td>
<td>4 (27%)</td>
<td>2 (13%)</td>
<td>1 (7%)</td>
<td>...</td>
<td>23</td>
<td>254</td>
<td>60</td>
<td>22</td>
<td>180</td>
<td>5.27</td>
</tr>
<tr>
<td>MCA branch</td>
<td>11</td>
<td>11 (100%)</td>
<td>6 (54%)</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
<td>2 (18%)</td>
<td>6</td>
<td>93</td>
<td>11</td>
<td>2</td>
<td>51</td>
<td>4.15</td>
</tr>
<tr>
<td>All patients</td>
<td>32</td>
<td>31 (97%)</td>
<td>14 (44%)</td>
<td>6 (19%)</td>
<td>4 (13%)</td>
<td>5 (16%)</td>
<td>3 (9%)</td>
<td>19</td>
<td>230</td>
<td>39</td>
<td>24</td>
<td>118</td>
<td>3.99</td>
</tr>
</tbody>
</table>

A: T2′ signal reduction in the affected hemisphere.
B: Occlusion type.
ΔT2′ indicates T2′ signal loss; S, level of significance. ADC lesion (L0), TTP lesion (T0), final infarct size (F5–8), LG, and ST. rt-PA indicates recombinant tissue plasminogen activator; MCA-trunc, MCA M1-segment.
day 0 (L0)), whereas the final infarct size was defined in F5–8. The ROI of the TTP–lesion day 0 (T0) revealed an estimate of the initial perfusion impairment. Lesion growth (LG) from day 0 to days 5 to 8 was derived by subtracting L0 from F5–8, and surviving tissue (ST) was calculated by subtracting F5–8 from T0. These ROIs are schematically visualized in Figure 1. All ROIs were outlined manually by experienced neuroradiologists (T.K., B.G.), and the volumes of the ROIs were recorded. Subsequently, the ROIs were transferred to the T2/H11032 images defining the voxels of interest. Relative side differences of T2/H11032 were calculated by comparison of the lesion ROIs with the mirrored ROIs of the contralateral side; these differences were consecutively analyzed by statistical testing (2-tailed t test with P<0.05; Software SPSS 10.0).

Results

We observed a clear decrease of the T2' values in the infarcted hemisphere (L0 and LG) compared with the unaffected control ROIs (mean of all voxels enclosed in an individual ROI; P<0.05 in 2-tailed t test). The mean value showed the most pronounced loss of T2' signal intensity in L0 (~15.7%), followed by a smaller decrease of T2' in LG (~10.5%; periphery of the ischemic core) and ST (~8.0%). These results are listed in the Table (A) and illustrated in Figure 2. Comparison of the mean absolute T2' values of the 3 ROIs in the affected hemisphere (L0 =126 ms; LG =132 ms; ST =120 ms) did not reveal statistical significant differences in 2-tailed t test (P>0.05 each).

Figure 3A through 3D representatively illustrates the T2' decrease in the case of a 59-year-old female patient 4.8 hours after symptom onset attributable to occlusion of the M1 segment of left MCA, followed by immediate thrombolysis. Infarction of the basal ganglia occurred on follow-up; however, the area of decreased T2' is considerably exceeding the initial ischemic core defined by the ADC decrease (L0) as well as the final infarct (F5–8), suggesting rescue of penumbral tissue. For the same patient, we plotted T2' histograms of the ROIs L0, LG, and ST (Figure 4A through 4C), revealing a shift toward lower T2' values in case of L0 and LG of the infarcted hemisphere; a smaller decrease of T2' was registered in ST.

As demonstrated in Figure 5A through 5F, another patient (54-year-old male) with acute ischemia 3.6 hours after symptom onset in the territory of the left MCA (occlusion of M1 segment; subsequent thrombolysis) showed a hyperperfusion in the occipital segment of the initial T0 in follow-up imaging on day 1 as result of a partial recanalization (Figure 5E). Strongly increased deoxy-Hb (low T2') was found in the area without recanalization on day 1, whereas highly decreased...
deoxy-Hb (high T2') could be detected in the hyperperfused area (Figure 5F). This indicates an oversupply of oxygenated hemoglobin in infarcted but futile perfused tissue without substantial oxygen utilization.

TOF angiography on day 0 revealed a carotid-T occlusion in 6, occlusion of the MCA in 15 (MCA trunk, MCA trifurcation), and occlusion of an MCA branch in 11 cases (Table, B). Recanalization was assessed according to the modified thrombolysis in myocardial infarction (TIMI) criteria for perfusion and vessel status. In cases of 3 patients, TOF angiography on day 1 failed because of movement artifacts. Using the volumes of the ROIs T0 (TTP delay on day 0) and F5–8 (final infarct size in the FLAIR image), we calculated an additional parameter q=T0/F5–8. A substantial

Figure 4. T2' histograms affected vs unaffected hemisphere. Same patient as in Figure 3. Shift toward lower T2' values in the ROIs L0 and LG of the affected hemisphere; smaller decrease in ST. A, ADC lesion (L0). B, LG. C, ST.
overestimation of the finally infarcted brain tissue by the initial TTP lesion is reflected by a median value of $q=3.99$ (Table, B; considered all 32 study patients).

**Discussion**

Applying quantitative BOLD imaging in acute stroke patients, we demonstrated a signal reduction in the T2$^*/$H1 images presumably corresponding with an increase of deoxy-Hb attributable to an increase of OEF. Hence, a more reliable metabolic description of the penumbra was possible in a larger patient group compared with the simple perfusion–diffusion mismatch, which frequently overestimates the final lesion. We demonstrated a relation of $\approx 4:1$ volume of TTP delay versus definitely infarcted tissue in this study ($q=T0/T0–8$). In a quantitative analysis, we found shortened T2$^*/$H1 values adjacent to the ADC lesion in the region later progressing to infarction (ROI LG), which represents the essential penumbra. This phenomenon might be explained by an increase of deoxy-Hb as a result of an elevated OEF caused by hypoperfusion in a region with still viable brain tissue. This explanation is in accordance with the current pathophysiological understanding and in line with previously published results. A considerable increase of OEF should occur in the penumbra, as suggested by positron emission tomography (PET) studies, and as a consequence, an increase of deoxy-Hb can be observed because of overextended primary compensation mechanisms such as vasodilatation.

Interestingly, the ischemic core defined by the ADC decrease (L0 on day 0) showed even more T2$^*$ shortening than LG, which has been operationally defined as the penumbra. In case of the ADC lesion with its assumed collapse, or at least strong reduction, of functional and structural neuronal metabolism, we would have expected a strongly reduced $O_2$ utilization, a clearly lowered OEF, a decreased deoxy-Hb, and consecutively an increased T2$^*$.

The concentration of deoxy-Hb in a single voxel is determined mainly by 2 factors: changes in the local generation of deoxy-Hb inside the voxel, and changes in the transport of deoxy-Hb into or out of the voxel. Combining PET and MRI in acute stroke imaging, recent research suggests that the ADC lesion may not only describe the ischemic core but can also include a considerable portion of penumbral tissue. This is supported by the finding that even severe ADC decreases do not predict irreversible tissue damage in humans. The acute ADC lesion may not only represent tissue destined to infarct but also severely ischemic tissue that still may be saved from pan-necrosis. A novel insight into the region of ADC decline in acute stroke using magnetic resonance spectroscopy shows a heterogeneous cellular metabolic injury within this region. These findings may explain a residual $O_2$ utilization inside the ADC lesion (L0), but still this might not implicate why the mean local generation of deoxy-Hb inside L0 should be greater than in LG.

Furthermore, the remaining deoxy-Hb in the ischemic core may serve as the main contributor to the low T2$^*$ in L0; previously produced deoxy-Hb cannot effectively be removed because of the highly reduced cerebral blood flow and may thus account for the T2$^*$ shortening. By PET imaging, the ischemic core is defined as the central region with strong OEF reduction. PET methodically does not detect deoxy-Hb directly and is dependent on the presence of labeled oxygen. However, the presence of oxygen is improbable in the nonperfused ischemic core; hence, there is no discrepancy between PET and T2$^*$ MRI.

In principle, estimates of the OEF and the cerebral metabolic rate of oxygen utilization (CMRO$_2$) are possible using BOLD MRI and PWI. However, we decided not to apply these extensive additional computations because PWI and the phenomena influencing the BOLD signal in acute ischemia are hardly controllable. The simple approximation of deoxy-Hb...
by T2’ imaging in acute stroke patients may suffice present clinical needs. Therefore, our findings are not directly comparable to those of Lee et al. In their study of hyperacute stroke patients, CMRO2 was calculated applying the formula: CMRO2= cerebral blood flow×OEF. Similar to our results, they found a CMRO2 reduction exceeding the ADC lesion in a few cases. Signal differences might be more pronounced in their approach, and the theoretical background may justify a similar estimation of the penumbra as defined by PET. Our approach also showed considerable T2’ decreases in regions outside the ADC lesion, later progressing to infarction (LG); but the large variety and SD did neither allow the estimation of a threshold nor the clear-cut delineation of the penumbral border. Absolute T2’ differences in the 3 ROIs analyzed (affected hemisphere) did not reveal statistical significance. We assume n=32 patients being too small and anatomical prerequisites (eg, low T2’ in the basal ganglia) introducing significant variance. The additional information of the ADC image still is needed to discriminate the infarct core from LG.

Nonetheless, BOLD MRI may contribute to our pathophysiological understanding. For example, the T2’ signal behavior of the patient shown in Figure 5 indicates heavily increased deoxy-Hb (low T2’ of the patient shown in Figure 5 indicates heavily increased deoxy-Hb) introducing significant variance. The additional information of the ADC image still is needed to discriminate the infarct core from LG.

Similar to L0 and LG, we detected a significant T2’ signal loss in the ROI ST of the affected hemisphere. As expected, this signal reduction was smaller than the reduction observed in L0 and LG. In our opinion, the signal loss is the result of a “benign” oligemia. Brain tissue described by ST is indeed experiencing hypoperfusion but is going to survive the acute stroke situation because of a timely recanalization of the occluded vessel (day 1 44% TIMI3; 19% TIMI2) or a good leptomeningeal collateralization, as proven in the follow-up MRI 1 week after stroke onset.

The calculated T2’ images show substantial echo-planar imaging artifacts, which are caused by the underlying T2* echo-planar triple-echo sequence. This results in a “wave-like” modulation of the signal intensity in the T2’ images not representing the deoxy-Hb effect and a consecutive worsening of the ROI statistics. These artifacts are strongest in the occipitopolar and frontopolar areas of the images and considerably smaller in the territory of the medial cerebral artery presenting the subject of investigation in this study. Nevertheless, it will be a challenge of future work to improve the characteristics of the T2* echo-planar imaging sequence to minimize the above-mentioned artifacts. The choice of only a few echoes may induce a methodical overestimation of T2, T2*, and T2’; however, this is not a problem of side-by-side comparisons, which reveal more valuable relative results.

Conclusions

The implementation of BOLD imaging in an acute stroke MRI protocol offers a noninvasive estimation of the O2 utilization and is able to provide additional information concerning the present metabolic state of the threatened brain tissue. The changes in T2’ intensity are visually noticeable in the reconstructed T2’ images and provide a better estimation of the real penumbra. Future studies should be undertaken to confirm the clinical value of this new approach and to optimize the MRI sequence technique.

Disclosures

None.

References

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