Effects of Cerebral Ischemia on Evoked Cerebral Blood Oxygenation Responses and BOLD Contrast Functional MRI in Stroke Patients

Yoshihiro Murata, MD, PhD; Kaoru Sakatani, MD, PhD; Tatsuya Hoshino, MD, PhD; Norio Fujiwara, MD, PhD; Tsuneo Kano, MD, PhD; Shin Nakamura, MD; Yoichi Katayama, MD, PhD

Background and Purpose—To evaluate the mechanisms of failure of blood oxygenation level–dependent (BOLD) imaging in stroke, we compared the evoked cerebral blood oxygenation (CBO) responses and activation volumes (AVs) of BOLD functional MRI (fMRI) in chronic stroke patients with moderate and severe cerebral ischemia.

Methods—We measured the evoked CBO responses in the primary sensorimotor cortex (PSMC) by means of near-infrared spectroscopy during contralateral motor tasks. We compared the AV of BOLD-functional MRI in the PSMC on the nonlesion and lesion sides. Single-photon emission computed tomography was used to classify ischemic status as moderate (slight reduction of regional cerebral blood flow and cerebrovascular reserve capacity [CVRC]) or severe (marked reduction of regional cerebral blood flow and CVRC; ie, misery perfusion).

Results—In age-matched controls, deoxyhemoglobin concentration decreased with concomitant increases in oxyhemoglobin and total hemoglobin concentrations during activation. The PSMC on the nonlesion side exhibited a normal CBO response pattern. On the lesion side, moderate cerebral ischemia did not affect the CBO response pattern, but severe cerebral ischemia caused an increase of deoxyhemoglobin during the task, associated with increases of oxyhemoglobin and total hemoglobin. Moderate cerebral ischemia induced only a slight reduction of the AV on the lesion side; however, severe cerebral ischemia markedly reduced the AV on the lesion side. The BOLD signal did not change in some areas of the PSMC on the lesion side in severe cerebral ischemia, whereas it tended to decrease in other areas during the tasks.

Conclusions—Misery perfusion caused a marked reduction of the AV on BOLD imaging, associated with an increase of deoxyhemoglobin concentration during activation. BOLD-fMRI investigations of stroke patients should be performed while giving consideration to baseline circulatory status. Functional near-infrared spectroscopy could be an alternative means to assess the CVRC. (Stroke. 2006;37:2514-2520.)

Key Words: blood oxygenation level dependent ■ cerebral blood flow ■ hemoglobin ■ near-infrared spectroscopy ■ oxygen metabolism ■ primary sensorimotor cortex
stroke patients exhibited a normal evoked CBO response pattern in the activated areas. In contrast, Sakatani et al.\textsuperscript{20} revealed that a number of chronic stroke patients exhibited an atypical evoked CBO response pattern (ie, an increase of deoxy-Hb associated with increases of oxy-Hb and t-Hb) in the left prefrontal cortex during language tasks. In addition, we observed similar atypical evoked CBO changes in the primary sensorimotor cortex (PSMC) of stroke patients during contralateral motor tasks.\textsuperscript{21} Interestingly, despite normal motor function, BOLD-fMRI showed small activation areas in the PSMC on the lesion side, suggesting that altered evoked CBO responses induced by cerebral ischemia cause a failure of BOLD imaging in stroke patients. However, the quantitative relations among cerebral ischemic levels, evoked CBO responses, and BOLD imaging remain unclear. In the present study, to clarify these issues, we evaluated the NIRS parameter values, the activation volumes (AVs), and BOLD signal changes on BOLD-fMRI in the PSMC during motor tasks in patients with different cerebral circulatory conditions (ie, age-matched controls and chronic stroke patients with moderate and severe cerebral ischemia).

**Methods**

**Subjects**

We studied 10 patients with cerebral ischemia (7 men, 3 women; mean±SD age, 52.5±9.9 years; range, 38.6-69.0 years) and 10 age-matched controls (8 men, 2 women; mean±SD age, 52.5±9.9 years; P>0.05). Nine patients had experienced multiple episodes of transient ischemic attack (TIA), whereas 1 patient had had a complete stroke (Table 1). The TIAs were attributable to hemodynamic compromise caused by occlusion of the internal carotid artery in 4 cases and of the middle cerebral artery (MCA) in 4 cases; the major symptom of TIA was motor paresis. The complete stroke was attributable to occlusion of the internal carotid artery, which caused transient motor paresis and persistent visual field defects; MRI demonstrated watershed infarction in the border region between the territory of the MCA and the posterior cerebral artery. Cerebral angiography demonstrated poor collateral circulation in all of the patients; single-photon emission tomography (SPECT) revealed reduced regional cerebral blood flow (rCBF) at rest and percentage cerebrovascular reserve (%CVR) response to acetazolamide (ACZ) in all patients (see Results). The examinations with BOLD-fMRI and NIRS were performed within 1 month after the last attack in all patients; the patients did not show motor paresis of the upper extremities at the time of examination. The age-matched controls had mild carotid stenosis (<50%), which was incidentally detected by ultrasonography during medical checkup but revealed no cerebral ischemia as detected by SPECT (see Results). The study was approved by the Committee for Clinical Trials and Research on Humans of Nihon University School of Medicine.

We evaluated rCBF at rest and %CVR response to ACZ (1.0) in the territory of the MCA with BOLD-fMRI (Prism 2000XP; Shimadzu Co)\textsuperscript{23} as follows: %CVR=[(rCBF<sub>ACZ</sub>−rCBF<sub>rest</sub>)/rCBF<sub>rest</sub>]<times>100, where rCBF<sub>ACZ</sub> and rCBF<sub>rest</sub> represent the rCBF before and after injection of ACZ, respectively.

**NIRS Measurements**

We measured the evoked CBO responses in the PSMC contralateral to the task performance with an NIRO-300 (Hamamatsu Photonics K.K.). The NIRS probes were positioned over the PSMC, as described by previously.\textsuperscript{21,23,24} In brief, the probes were placed 3 cm apart on the head over the PSMC so that the axes of the probes could be aimed be superimposed on the central sulcus. The location of the probes was identified by MRI and administration of vitamin E capsules.

We measured the evoked CBO responses in the PSMC on the nonlesion and the lesion side during contralateral hand-grasping tasks. The task paradigm consisted of 40 seconds of rest and 40 seconds of self-paced hand grasping; this task-rest cycle was repeated 6 times. We observed the task performance of all subjects during the experiments; the frequency of hand grasping was approximately once per second. The stroke patients could perform the motor task similarly to the control subjects at the time of the examination.

**BOLD-fMRI**

We obtained functional images during hand-grasping tasks similar to those seen in our previous BOLD-fMRI studies.\textsuperscript{21,24} The BOLD-fMRI signals were measured with a 1.5-T MRI (Symphony; Siemens) and use of an echoplanar technique (echo time, 50 ms; repetition time, 4 sec; slice thickness, 3 mm; matrix size, 40×40; field of view, 192×40192 mm); 120 frames of 40 axial slices (acquisition time of 1 frame, 4 seconds) through the PSMC were acquired during repeated motor task periods (40 seconds) and resting periods (40 seconds). The task paradigm was the same as the one used in the NIRS measurements. Activation maps were calculated by statistical parametric mapping (SPM; z score >1.5). We used the BrainVoyager 2000 system (Brain Innovation BV) for analysis of the BOLD signal changes.

**Data Analysis**

We evaluated the changes in oxy-Hb, deoxy-Hb, and t-Hb by subtracting the mean baseline values (40 seconds) from the mean stimulation values (40 seconds). Comparisons were made for each of

---

**TABLE 1. Clinical Profiles and Cerebral Ischemic Status of the Stroke Patients**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Clinical Type of Stroke</th>
<th>Cause of Stroke</th>
<th>Side of Lesion</th>
<th>MRI</th>
<th>rCBF at Rest, mL·100 g&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>%CVR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>TIA</td>
<td>ICAo</td>
<td>L</td>
<td>N</td>
<td>34.6</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>47/M</td>
<td>TIA</td>
<td>ICAo</td>
<td>L</td>
<td>N</td>
<td>32.1</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>71/M</td>
<td>TIA</td>
<td>MCAo</td>
<td>R</td>
<td>N</td>
<td>35.2</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>55/F</td>
<td>TIA</td>
<td>ICAo</td>
<td>L</td>
<td>N</td>
<td>32.1</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>51/M</td>
<td>TIA</td>
<td>ICAo</td>
<td>L</td>
<td>N</td>
<td>33.2</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>71/M</td>
<td>TIA</td>
<td>MCAo</td>
<td>R</td>
<td>N</td>
<td>34.4</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>65/F</td>
<td>TIA</td>
<td>MCAo</td>
<td>R</td>
<td>N</td>
<td>24.0</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>49/M</td>
<td>TIA</td>
<td>MCAo</td>
<td>L</td>
<td>N</td>
<td>23.9</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>49/F</td>
<td>CS</td>
<td>ICAo</td>
<td>R</td>
<td>Cl</td>
<td>25.1</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>68/M</td>
<td>TIA</td>
<td>ICAo</td>
<td>R</td>
<td>N</td>
<td>22.6</td>
<td>10</td>
</tr>
</tbody>
</table>

CS indicates complete stroke; ICAo, occlusion of the internal carotid artery; MCAo, occlusion of the middle cerebral artery; Cl, cerebral infarction; N, normal.
the NIRS parameters with paired t tests. \( P<0.05 \) was defined as the criterion of significant difference.

We calculated the AVs in the PSMC on the nonlesion and lesion side by counting the activated voxels in these areas, which were normalized to the AVs on the nonlesion side (ie, AVs on the lesion side/AVs on the nonlesion side). We used the Mann–Whitney \( U \) test for comparison of the normalized AVs between the stroke patients and age-matched controls. In addition, we evaluated the correlation between the normalized AVs and rCBF at rest, %CVR, and deoxy-Hb with Spearman correlation coefficient by rank test.

### Results

The cerebral ischemic conditions of the patients could be classified into moderate cerebral ischemia (6 patients; slight reduction of baseline rCBF: 32.2 to 35.2 \( \text{mL} \cdot \text{100 g}^{-1} \cdot \text{min}^{-1} \)) and %CVR (7% to 12%) and severe cerebral ischemia (4 patients; marked reduction of baseline rCBF: 22.6 to 25.1 \( \text{mL} \cdot \text{100 g}^{-1} \cdot \text{min}^{-1} \)) and %CVR (−2% to −10%). There were significant differences in baseline rCBF and %CVR between the moderate and severe cerebral ischemia groups (Table 2).

In the age-matched controls, the motor task consistently caused a decrease of deoxy-Hb with increases of oxy-Hb and t-Hb in the contralateral PSMC (Figure 1A). BOLD-fMRI demonstrated robust activation areas in the PSMC during the task (Figure 1C). In both of the ischemia groups, the PSMC on the nonlesion side exhibited a normal evoked CBO response pattern and robust activation areas on BOLD-fMRI during the contralateral motor task (Figure 1B and 1D).

In the moderate cerebral ischemia group, the evoked CBO response pattern on the lesion side was similar to that in the control subjects (Figure 2A; case No. 1); however, in the severe cerebral ischemia group, the deoxy-Hb concentrations increased during the entire course of the task concomitantly with increases of oxy-Hb and t-Hb (Figure 2B, case No. 8). There were significant differences in NIRS parameters between the controls, the moderate cerebral ischemia group, and the severe cerebral ischemia group (Table 3). The degrees of decrease of deoxy-Hb and of increase of oxy-Hb and t-Hb in the moderate cerebral ischemia group were significantly smaller than those in the control subjects. In addition, the degrees of increase of oxy-Hb and t-Hb in the severe cerebral ischemia group were significantly smaller than those in the moderate cerebral ischemia group; the increase of deoxy-Hb in the severe cerebral ischemia group significantly differed from the decrease of deoxy-Hb in the moderate cerebral ischemia group. There were no significant differences in NIRS parameters between patients with right artery occlusion and those with left artery occlusion.

BOLD-fMRI clearly demonstrated activation areas on the lesion side in the moderate cerebral ischemia group (Figure 2C); however, the normalized AV in the moderate cerebral ischemia group (0.72±0.12%) was slightly but significantly smaller than that in the age-matched controls (1.02±0.10; \( P<0.01 \)). In the severe cerebral ischemia group, BOLD-fMRI demonstrated only small activation areas (Figure 2D). The

![Figure 1](https://stroke.ahajournals.org/figure1)

**Figure 1.** Evoked CBO responses in the PSMC and activation maps of BOLD-fMRI during contralateral motor tasks. A and B, Evoked CBO responses in the PSMC on the right side in an age-matched control subject and on the nonlesion side in a severe cerebral ischemia patient (No. 8). C and D, Activation maps of BOLD-fMRI in the age-matched control subject and severe cerebral ischemia patient. The ordinates indicate the concentration changes of the NIRS parameters in arbitrary units. The horizontal thick bars denote the task period (40 seconds).
normalized AV in the severe cerebral ischemia group (0.19±0.06%) was significantly smaller than that of the moderate cerebral ischemia group (P<0.01); no significant differences in normalized AVs were observed between patients with right artery occlusion and those with left artery occlusion. Also, significant correlations between the normalized AV and baseline rCBF (P<0.01) and %CVR (P<0.01) were observed (Figure 3). We found that t-Hb showed significant positive correlations with rCBF (P<0.01), %CVR (P<0.01), and normalized AV (P<0.01; Figure 4A through 4C). In addition, deoxy-HB showed significant negative correlations with rCBF (P<0.01), %CVR (P<0.01), and normalized AV (P<0.01) (Figure 4D through 4F).

The BOLD signal increased consistently during the tasks in the PSMC on the nonlesion side in severe cerebral ischemia, whereas NIRS showed a decrease of deoxy-Hb. In contrast, the BOLD signal did not increase consistently during the tasks in the PSMC on the lesion side, whereas BOLD-fMRI did not identify neuronal activation, but NIRS showed increases of deoxy-Hb (Figure 5). Note that the BOLD signal did not change in some areas of the PSMC, although it tended to decrease in other areas during the tasks.

### Table 3. Comparison of NIRS Parameters in the Age-Matched Controls, Moderate Cerebral Ischemia Group, and Severe Cerebral Ischemia Group

<table>
<thead>
<tr>
<th></th>
<th>deoxy-Hb</th>
<th>oxy-Hb</th>
<th>t-Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-matched controls, n=10</td>
<td>−0.55±0.10</td>
<td>6.37±0.46</td>
<td>5.82±0.47</td>
</tr>
<tr>
<td>Moderate ischemia group, n=6</td>
<td>−0.40±0.08*</td>
<td>5.01±0.70†</td>
<td>4.61±0.68‡</td>
</tr>
<tr>
<td>Severe ischemia group, n=4</td>
<td>0.80±0.21§</td>
<td>2.07±0.25#</td>
<td>2.86±0.13¶</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.

*P<0.002, †P<0.003, ‡P<0.002 compared with age-matched controls; §P<0.003, #P<0.002, ¶P<0.003 compared with age-matched controls.

### Discussion

The present results demonstrate that cerebral ischemia affects the evoked CBO response patterns and BOLD imaging, depending on the level of ischemia. That is, moderate cerebral ischemia caused a slight reduction of the AV on BOLD imaging without affecting the evoked CBO response pattern, whereas severe cerebral ischemia caused an increase in the deoxy-Hb concentration during activation and a marked reduction of the AV. The severe cerebral ischemia is considered likely to correspond to stage 2 hemodynamic failure as classified by Powers et al (ie, "misery perfusion"), whereas the moderate cerebral ischemia might correspond to a circulatory condition between stages 2 and 1.

The moderate cerebral ischemia group exhibited a normal evoked CBO response pattern14-18; however, in the severe cerebral ischemia group, the deoxy-Hb concentration increased during activation concomitantly with increases of oxy-Hb and t-Hb. The increase of deoxy-Hb was evident during the entire course of the task and was distinct from the deoxy-Hb rise occurring within a few seconds after the start of neuronal activation.27 Increases of oxy-Hb and t-Hb during activation imply an increase of rCBF in response to neuronal activation. Thus, despite impairment of the cerebrovascular reserve capacity (CVRC), the vasodilatation response to neuronal activation must be preserved. This finding is consistent with a previous positron emission tomography study of stroke.28 However, the degree of vasodilatation might be smaller in the severe cerebral ischemia group than in the moderate cerebral ischemia group, because the increase of t-Hb in the severe cerebral ischemia group was smaller than that in the moderate cerebral ischemia group. The atypical evoked CBO response has also been observed in brain tumor patients24 and newborn infants.29

The physiological mechanism of the deoxy-Hb increase during activation should be considered from the viewpoint of hemodynamic effects and oxygen metabolism. That is, the
reduced rCBF and impaired CVRC under resting conditions could cause a lesser degree of rCBF rise during activation, resulting in a decrease of the driving force to "wash out" deoxy-Hb in the capillaries and veins. When such an impairment of the hemodynamic response is advanced, oxygen extraction could increase owing to a decrease of oxygen delivery during activation. Quantitative models of oxygen delivery during activation predict that disproportionately large increases of rCBF are required for small increases of oxygen consumption. Thus, a small decrease in the evoked rCBF response can cause oxygen deficiency during activation. These alterations in the hemodynamic effects and oxygen metabolism could lead to a lesser decrease or elevation of the deoxy-Hb concentrations in the vessels.

The moderate cerebral ischemia caused a slight reduction of the AV in BOLD-fMRI on the lesion side compared with the nonlesion side without affecting the evoked CBO response pattern. This slight reduction of AVs might have been caused by a possible smaller decrease of the deoxy-Hb concentration during activation (see earlier discussion of the hemodynamic effects on deoxy-Hb) because a smaller decrease of the paramagnetic deoxy-Hb concentration could
reduce the BOLD signal rise.\textsuperscript{11,30,31} Indeed, several studies have reported that the magnitudes of BOLD signal changes are small in stroke patients.\textsuperscript{4–10}

In the severe cerebral ischemia group, BOLD-fMRI disclosed significantly small AVs in the PSMC on the lesion side. Recent BOLD-fMRI studies in stroke patients have revealed a similar failure of BOLD imaging in such patients.\textsuperscript{4–10} We suggest that the failure of BOLD imaging might be caused by the atypical evoked CBO response (ie, increases of both deoxy-Hb and t-Hb), which have opposite effects on the BOLD signal change. That is, an increase of t-Hb (ie, CBV) increases the water fraction around the deoxy-Hb molecules in a given voxel, leading to an increase of the BOLD signal, whereas an increase of the paramagnetic deoxy-Hb concentration tends to decrease the BOLD signal.\textsuperscript{11,30,31} Such opposite effects of deoxy-Hb and t-Hb on the BOLD signal could lead to a marked reduction of AV. Indeed, we observed a negative correlation between deoxy-Hb and AV and a positive correlation between t-Hb and AV.

The relation between the BOLD signal and the evoked CBO responses in the pathological brain may differ from that in the normal brain. Hess et al\textsuperscript{31} observed positive BOLD signals in the gerbil barrel cortex, where optical imaging demonstrated increases of deoxy-Hb and t-Hb during activation. However, in the present study, the BOLD signal did not increase consistently during the motor tasks in the PSMC on the lesion side in severe ischemia, whereas NIRS showed increases of deoxy-Hb and t-Hb. In the PSMC, the BOLD signal did not change in some areas whereas it tended to decrease in other areas during the tasks. Such a decrease of the BOLD signal might be caused by an increase of deoxy-Hb in the cortical areas; however, the spatial resolution of NIRS is not high enough to distinguish the areas with BOLD signal increases from those without BOLD signal changes. We have observed a similar decrease of BOLD signals in the PSMC of a glioma patient after resection of the tumor; NIRS indicated increases of deoxy-Hb and t-Hb during activation.\textsuperscript{32} Such a paradoxical decrease of the BOLD signal has also been observed in a stroke patient.\textsuperscript{7} In addition, an fMRI study in rat stroke models has demonstrated that, compared with the normal cortex, the affected cortex revealed a lower covariance between activated voxels by BOLD and CBV-weighted fMRI during stroke recovery.\textsuperscript{33} Finally, unlike the normal brain, the pathological brain may exhibit heterogeneous evoked CBO changes in the activated cortex. In our recent study on brain tumors, we observed that cortical areas with and without increases of the BOLD signal coexisted in the activated PSMC, which was confirmed by intraoperative cortical mapping.\textsuperscript{24} Although the present study did not evaluate the activation of the PSMC directly, the difference in BOLD signal changes in the PSMC in severe cerebral ischemia suggests heterogeneity of evoked CBO changes in the ischemic brain.

In conclusion, the baseline cerebral ischemic condition, particularly misery perfusion, affects the evoked CBO response pattern and impairs BOLD imaging in stroke patients. BOLD-fMRI should therefore be performed in stroke patients while giving consideration to the baseline cerebral circulatory status at the time of examination. Monitoring of evoked CBO responses by NIRS may be useful for avoiding possible misinterpretation. Finally, NIRS measurements of evoked CBO responses may provide a safe means of assessing the CVRC in stroke patients without administration of ACZ.

Sources of Funding
This work was supported by a grant-in-aid from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan (A12307029) and a grant from Hamamatsu Photonics K.K. (Hamamatsu, Japan).

Disclosures
None.

References
Effects of Cerebral Ischemia on Evoked Cerebral Blood Oxygenation Responses and BOLD Contrast Functional MRI in Stroke Patients
Yoshihiro Murata, Kaoru Sakatani, Tatsuya Hoshino, Norio Fujiwara, Tsuneo Kano, Shin Nakamura and Yoichi Katayama

Stroke. 2006;37:2514-2520; originally published online August 31, 2006; doi: 10.1161/01.STR.0000239698.50656.3b

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/37/10/2514

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/