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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

Blood oxygenation level–dependent (BOLD) contrast functional magnetic resonance imaging (BOLD-fMRI) has been used in functional studies of stroke patients, with the assumption that these patients have normal neurovascular coupling.[1–3] Recent studies have revealed, however, that BOLD-fMRI does not correctly image activation areas in stroke patients.[4–10] It was suggested that impairments of neurovascular coupling may alter the evoked cerebral blood oxygenation (CBO) responses and hemodynamic changes, and this could result in failure of BOLD imaging in stroke patients. BOLD-fMRI alone, however, cannot elucidate the precise mechanisms for the failure of BOLD imaging, because BOLD-fMRI provides information mainly about concentration changes of deoxyhemoglobin (deoxy-Hb), which is paramagnetic.[11,12]

In contrast, near-infrared spectroscopy (NIRS) measures concentration changes of not only deoxy-Hb but also oxyhemoglobin (oxy-Hb),[13] and changes in total hemoglobin (sum of oxy-Hb and deoxy-Hb; t-Hb) indicate cerebral blood volume (CBV) changes. NIRS studies of normal adults have revealed that neuronal activation generally causes a decrease of deoxy-Hb with increases of oxy-Hb and t-Hb in the activated cortical area,[14–18] and this is consistent with the physiological basis of BOLD imaging.[11,12] Indeed, simultaneous measurements of NIRS and BOLD-fMRI have demonstrated correlations between NIRS parameters and the BOLD signal.[19]

NIRS studies of chronic stroke patients have provided conflicting data concerning the evoked CBO response patterns.[3,20–22] Kato et al[3] and Miyai et al[22] found that chronic

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stroke patients exhibited a normal evoked CBO response pattern in the activated areas. In contrast, Sakatani et al[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.[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, 58.2±9.6 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 circulations 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 SPECT (Prism 2000XP; Shimadzu Co)[23] as follows: $\%CVR=[(rCBF_{ACZ}-rCBF_{rest})/rCBF_{rest}]\times 100$, where $rCBF_{ACZ}$ and $rCBF_{rest}$ 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.[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.[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

Case No.	Age, y/Sex	Clinical Type of Stroke	Cause of Stroke	Side of Lesion	MRI	rCBF at Rest, mL · 100 g^{-1} · min^{-1}	%CVR, %
1	56/M	TIA	ICAo	L	N	34.6	12
2	47/M	TIA	ICAo	L	N	32.1	7
3	71/M	TIA	MCAo	R	N	35.2	9
4	55/F	TIA	ICAo	L	N	32.1	10
5	51/M	TIA	ICAo	L	N	33.2	9
6	71/M	TIA	MCAo	R	N	34.4	10
7	65/F	TIA	MCAo	R	N	24.0	−2
8	49/M	TIA	MCAo	L	N	23.9	−4
9	49/F	CS	ICAo	R	CI	25.1	−5
10	68/M	TIA	ICAo	R	N	22.6	−10

CS indicates complete stroke; ICAo, occlusion of the internal carotid artery; MCAo, occlusion of the middle cerebral artery; CI, cerebral infarction; N, normal.

TABLE 2. Baseline rCBF and %CVR in the Age-Matched Controls, Moderate Cerebral Ischemia Group, and Severe Cerebral Ischemia Group

	Baseline rCBF, mL · 100 g^{-1} · min^{-1}	CVR, %
Age-matched controls, n=10	48.7±2.2	29.4±2.4
Moderate ischemia group, n=6	34.0±1.6*	9.1±4.4†
Severe ischemia group, n=4	23.9±3.4‡	−5.4±3.4§

Data are expressed as mean±SD.

*$P<0.001$, †$P<0.001$ compared with age-matched controls; ‡$P<0.01$, §$P<0.01$ compared with moderate cerebral ischemia group.

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).[24] We used the Mann–Whitney *U* test for comparison of the normalized AVs between the stroke patients and age-matched controls.

We evaluated the statistical significance of differences in baseline rCBF and %CVR measurements between the stroke patients and age-matched controls by the Mann–Whitney *U* test. 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 mL · 100 g^{-1} · min^{-1}) and %CVR (7% to 12%) and severe cerebral ischemia (4 patients; marked reduction of baseline rCBF: 22.6 to 25.1 mL · 100 g^{-1} · 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

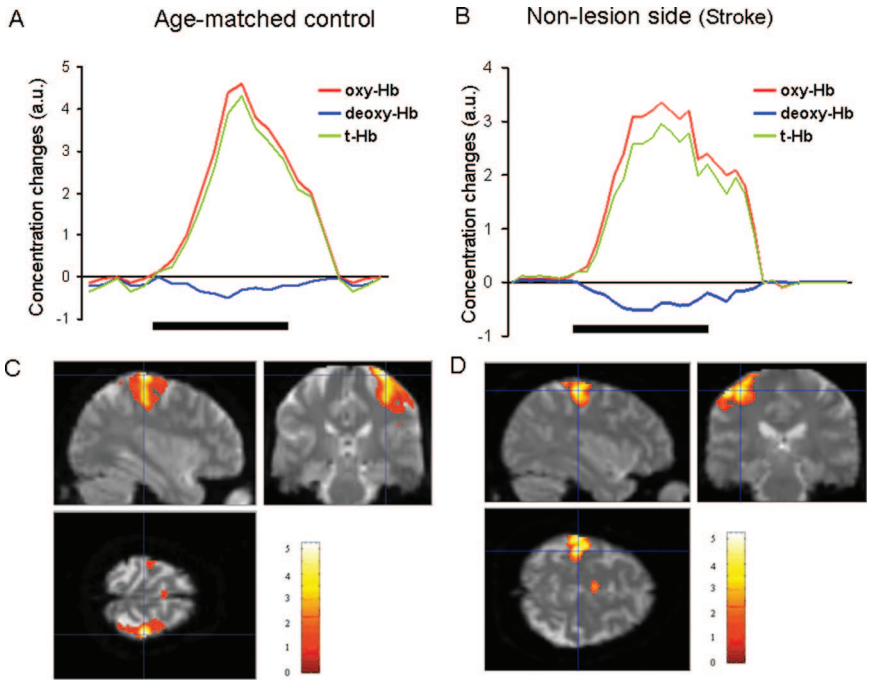

Figure 1. Evoked CBO responses in the PSMC and activation maps of BOLD-fMRI during contralateral motor tasks. A and B, Evoked CBO responses in the PSMC on the right side in an age-matched control subject and on the nonlesion side in a severe cerebral ischemia patient (No. 8). C and D, Activation maps 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).

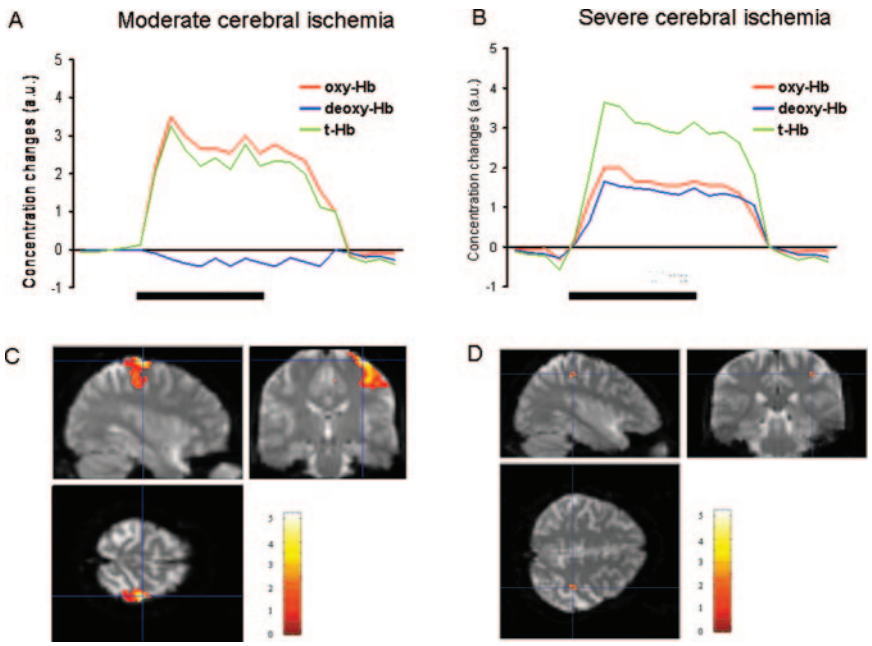

Figure 2. Comparison of evoked CBO responses in the PSMC on the lesion side and activation maps of BOLD-fMRI between patients with moderate cerebral ischemia and severe cerebral ischemia. A and B, Evoked CBO responses in moderate cerebral ischemia (case No. 1) and severe cerebral ischemia (case No. 8). C and D, Activation maps in moderate cerebral ischemia and severe cerebral ischemia patients. The ordinates indicate the changes of the NIRS parameters in arbitrary units. The horizontal thick bars denote the task period (40 seconds). Note that, in the severe cerebral ischemia patient, NIRS demonstrated an increase of deoxy-Hb with increases of oxy-Hb and t-Hb during the task; BOLD-fMRI imaged only a small activation area.

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

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

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"),[25] whereas the moderate cerebral ischemia might correspond to a circulatory condition between stages 2 and 1.[26]

The moderate cerebral ischemia group exhibited a normal evoked CBO response pattern[14–18]; 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 patients[24] 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

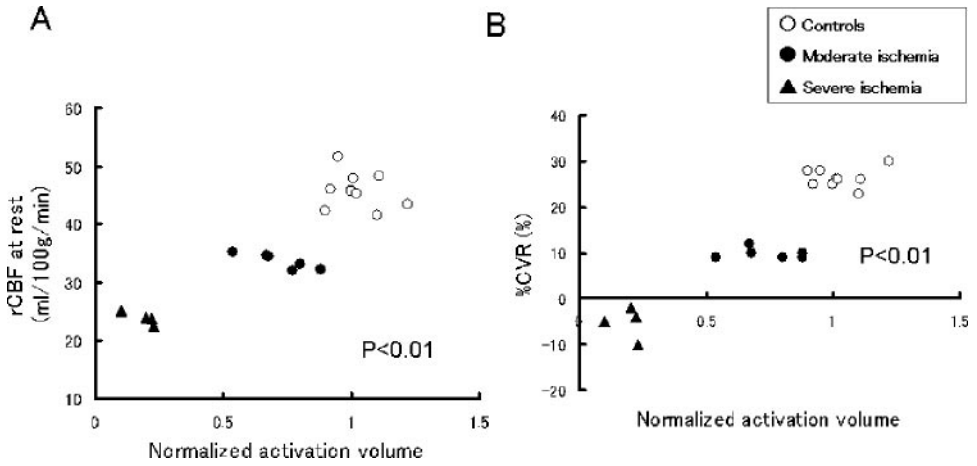

Figure 3. Correlations between the normalized AV of BOLD-fMRI and the rCBF at rest (A) and %CVR (B). Significant positive correlations were observed for both rCBF at rest ($P<0.01$) and %CVR ($P<0.01$).

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.[30] 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

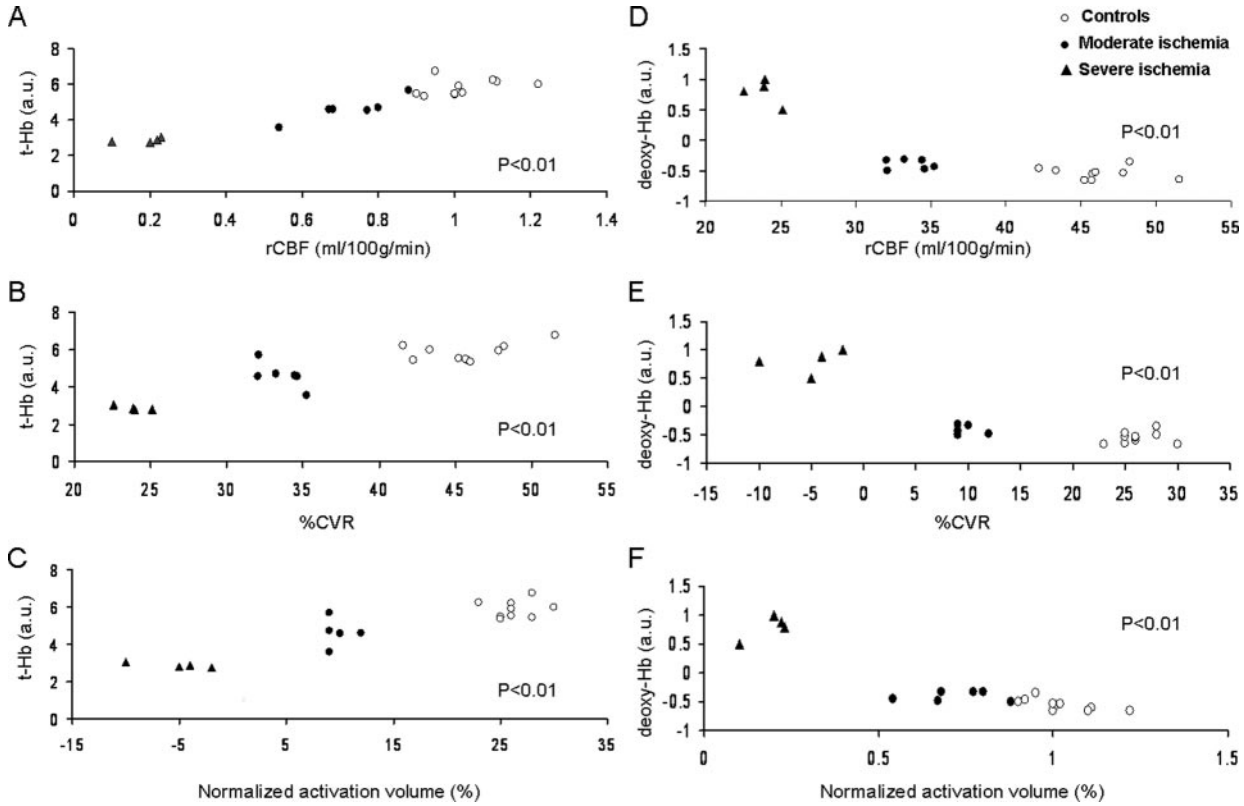

Figure 4. Correlations between t-Hb and rCBF at rest (A), between t-Hb and %CVR (B), and between t-Hb and normalized AV (C); a significant positive correlation was found in each case ($P<0.01$). Correlations between deoxy-Hb and rCBF at rest (D), between deoxy-Hb and %CVR (E), and between deoxy-Hb and normalized AV (F); a significant negative correlation was found in each case ($P<0.01$). The open circle, closed circle, and closed triangle indicate the age-matched controls, moderate cerebral ischemia group, and severe cerebral ischemia group, respectively.

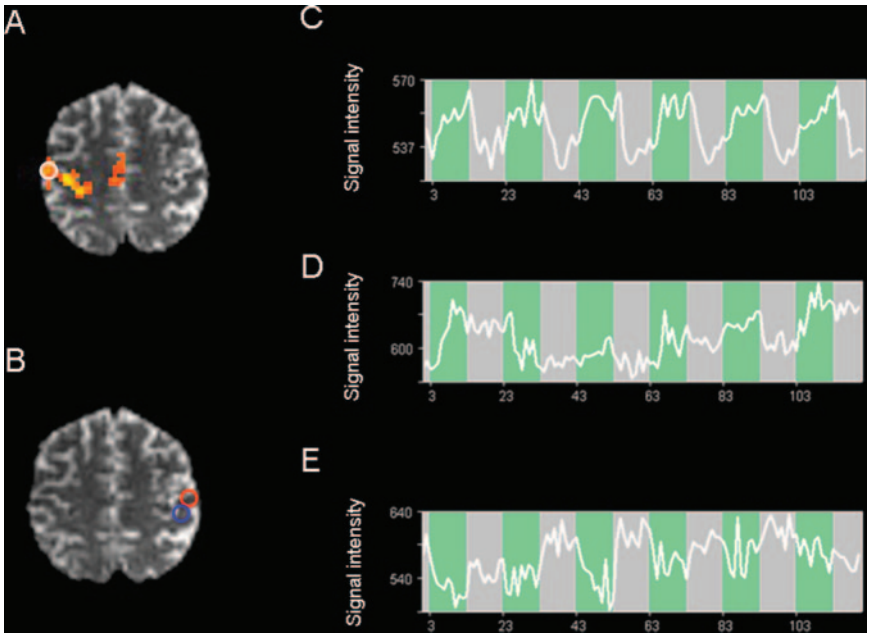

Figure 5. Comparison of BOLD signal changes in the PSMC on the nonlesion side and lesion side in severe cerebral ischemia. A and B, Activation maps for the left grasping task (nonlesion side (A) and the right grasping task (lesion side; B) in a severe cerebral ischemia patient (No. 8); the circles indicate the region of interest for analysis of the BOLD signal changes. C–E, Time courses of BOLD signal changes in the PSMC on the nonlesion side (C corresponds to the white circle in A) and lesion side (D and E correspond to the red and blue circles in B, respectively). Blue zones indicate task periods.

reduce the BOLD signal rise.[11,30,31] Indeed, several studies have reported that the magnitudes of BOLD signal changes are small in stroke patients.[4,7,9,10]

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.[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.[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[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.[32] Such a paradoxical decrease of the BOLD signal has also been observed in a stroke patient.[5] 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.[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.[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.

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Disclosures

None.

References

1. Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, Kennedy DN, Finklestein SP, Rosen BR. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*. 1997;28:2518–2527.

2. Cao Y, D'Olhaberriague L, Vikingstad EM, Levine SR, Welch KMA. Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis. *Stroke*. 1998;29:112–122.
3. Kato H, Izumiyama M, Koizumi H, Takahashi A, Itoyama Y. Near-infrared spectroscopic topography as a tool to monitor motor reorganization after hemiparetic stroke: a comparison with functional MRI. *Stroke*. 2002;33:2032–2036.
4. Pineiro R, Pendlebury S, Johansen-Berg H, Matthews PM. Altered hemodynamic responses in patients after subcortical stroke measured by functional MRI. *Stroke*. 2002;33:103–109.
5. Röther J, Knab R, Hamzei F, Fiehler J, Reichenbach JR, Buchel C, Weiller C. Negative dip in BOLD fMRI is caused by blood flow-oxygen consumption uncoupling in humans. *NeuroImage*. 2002;15:98–102.
6. D'Esposito M, Deouell LY, Gazzaley A. Alterations in the BOLD fMRI signal with aging and disease: a challenge for neuroimaging. *Nat Rev Neurosci*. 2003;4:863–872.
7. Hamzei F, Knab R, Weiller C, Rother J. The influence of extra- and intracranial artery disease on the BOLD signal in FMRI. *NeuroImage*. 2003;20:1393–1399.
8. Rossini PM, Altamura C, Ferretti A, Vernieri F, Zappasodi F, Caulo M, Pizzella V, Del Gratta C, Romani GL, Tecchio F. Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain*. 2004;127:99–110.
9. Binkofski F, Seitz RJ. Modulation of the BOLD-response in early recovery from sensorimotor stroke. *Neurology*. 2004;63:1223–1229.
10. Krainik A, Hund-Georgiadis M, Zysset S, von Cramon DY. Regional impairment of cerebrovascular reactivity and BOLD signal in adults after stroke. *Stroke*. 2005;36:1146–1152.
11. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A*. 1990;87:9868–9872.
12. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci U S A*. 1992;89:5951–5955.
13. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science*. 1977;198:1264–1267.
14. Hoshi Y, Tamura M. Detection of dynamic changes in cerebral oxygenation coupled to neuronal function during mental work in man. *Neurosci Lett*. 1993;150:5–8.
15. Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U. Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. *Neurosci Lett*. 1993;14:101–104.
16. Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, Frahm J. Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *J Cereb Blood Flow Metab*. 1996;16:817–826.
17. Villringer A, Chance B. Non-invasive optical spectroscopy and imaging of human brain function. *Trends Neurosci*. 1997;20:435–442.
18. Sakatani K, Lichty W, Xie Y, Li S, Zuo H. Effects of aging on language-activated cerebral blood oxygenation changes of the left prefrontal cortex: near infrared spectroscopy study. *J Stroke Cerebrovasc Dis*. 1999;8:398–403.
19. Huppert TJ, Hoge RD, Diamond SG, Franceschini MA, Boas DA. A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. *NeuroImage*. 2006;29:368–382.
20. Sakatani K, Xie Y, Lichty W, Li S, Zuo H. Language-activated cerebral blood oxygenation and hemodynamic changes of the left prefrontal cortex in poststroke aphasic patients: a near infrared spectroscopy study. *Stroke*. 1998;29:1299–1304.
21. Murata Y, Sakatani K, Katayama Y, Fukaya C. Increase in focal concentration of deoxyhemoglobin during neuronal activity in cerebral ischemic patients. *J Neurol Neurosurg Psychiatry*. 2002;73:182–184.
22. Miyai I, Yagura H, Hatakenaka M, Oda I, Konishi I, Kubota K. Longitudinal optical imaging study for locomotor recovery after stroke. *Stroke*. 2003;34:2866–2870.
23. Murata Y, Katayama Y, Sakatani K, Fukaya C, Kano T. Evaluation of extracranial-intracranial arterial bypass function by using near-infrared spectroscopy. *J Neurosurg*. 2003;99:304–310.
24. Fujiwara N, Sakatani K, Katayama K, Murata Y, Fukaya C, Yamamoto T. Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. *NeuroImage*. 2004;21:1464–1471.
25. Powers WJ, Press GA, Grubb RL Jr, Gado M, Raichle ME. The effect of hemodynamically significant carotid artery disease on the hemodynamic status of the cerebral circulation. *Ann Intern Med*. 1987;106:27–35.
26. Hirano T, Minematsu K, Hasegawa Y, Tanaka Y, Hayashida K, Yamaguchi T. Acetazolamide reactivity on ^{123}I-IMP single photon emission computed tomography in patients with major cerebral artery occlusive disease: correlation with positron emission tomography parameters. *J Cereb Blood Flow Metab*. 1994;14:763–770.
27. Malonek D, Grinvald A. Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain imaging. *Science*. 1996;272:551–554.
28. Inao S, Tadokoro M, Nishino M. Neural activation of the brain with hemodynamic insufficiency. *J Cereb Blood Flow Metab*. 1998;18:960–967.
29. Sakatani K, Saying C, Wemara L, Zuo H, Wang Y. Cerebral blood oxygenation changes induced by auditory stimulation in newborn infants measured by near-infrared spectroscopy. *Early Hum Dev*. 1999;55:229–236.
30. Boxerman JI, Bandettini PA, Kwong KK, Baker JR, Davis TL, Rosen BR, Weisskopf RM. The intravascular contribution to fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo. *Magn Reson Med*. 1995;34:4–10.
31. Hess A, Stiller D, Kaulisch T, Heil P, Scheich H. New insights into the hemodynamic blood oxygenation level-dependent response through combination of functional magnetic resonance imaging and optical recording in gerbil barrel cortex. *J Neurosci*. 2000;20:3328–3338.
32. Murata Y, Sakatani Y, Katayama Y, Fujiwara N, Fukaya C, Yamamoto T. Decreases of blood oxygenation level-dependent signal in the activated motor cortex during functional recovery after resection of a glioma. *Am J Neuroradiol*. 2004;25:1242–1246.
33. Kim YR, Huang IJ, Lee SR, Tejima E, Mandeville JB, van Meer MP, Dai G, Choi YW, Dijkhuizen RM, Lo EH, Rosen BR. Measurements of BOLD/CBV ratio show altered fMRI hemodynamics during stroke recovery in rats. *J Cereb Blood Flow Metab*. 2005;25:820–829.