

Motor-Related Intracortical Steal Phenomenon Detected by Multichannel Functional Near-Infrared Spectroscopy Imaging

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Key Words

Near-infrared spectroscopy · Ischemia · Steal phenomenon · Internal carotid artery stenosis

Abstract

Background: Patients with severe cerebral ischemia may lose autoregulation to increase cerebral blood flow following neural activity. Although the steal phenomenon under conventional cerebral blood flow study has been known as a high-risk factor for stroke, the cerebral oxygen hemodynamics in ischemic patients during functional activation has not been thoroughly investigated. In this study, we present rare cases with intracortical steal phenomenon during motor tasks detected by multichannel functional near-infrared spectroscopy before and after surgery. **Methods:** The relative concentration change of oxygenated, deoxygenated and total hemoglobin in and around the primary sensorimotor cortex during contralateral hand grasping was investigated in 11 patients with severe internal carotid artery stenosis. **Results:** In 3 patients, the concentration of total hemoglobin around the primary sensorimotor cortex significantly decreased in response to motor stimulation and returned to baseline soon after termination of the motor task. This phenomenon partially disappeared postopera-

tively in all patients who underwent surgery. The remaining 8 patients showed no signs of total hemoglobin decrease in and around the sensorimotor cortex. In 9 patients, lack of decrease in deoxygenated hemoglobin in the center of the primary motor cortex during the motor task was observed and 3 of them showed significant increase in deoxygenated hemoglobin. **Conclusions:** We have demonstrated that in some patients with severe ischemia, an abnormal motor-related steal phenomenon can be observed. This phenomenon can be modulated by surgical intervention and might imply the severity of ischemia.

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Introduction

It is widely accepted that neural activities are followed by changes in the regional oxygenation required for the oxygen consumption of neural cells and consisting of the supply of oxygenated blood from cerebral vessels into neural cells [1]. An increase in regional cerebral blood flow (rCBF) several times greater than needed has been reported in a positron emission computed tomography (PET) study [2], which constitutes the basis of functional neuroimaging utilizing the hemodynamic response to stimula-

tion. In the adjacent cortex where neural activities responding to the stimulation do not occur, a relatively low level of rCBF increase might take place due to spatially coarse regulation of local blood flow [3], but a decrease in rCBF has not been reported in normal healthy adults.

Near-infrared spectroscopy (NIRS) is a relatively novel functional monitoring modality which measures hemoglobin concentration in the capillary beds of the cerebral cortex based on the capability of near-infrared light to pass through the scalp and skull [4]. This methodology has been utilized not only to measure the resting oxygenation status of the cerebral cortex, but has also been utilized in functional neuroimaging (fNIRS imaging) which measures and compares the value of hemoglobin concentration in the activated cortex versus the surrounding nonactivated cortex [5–8].

In some patients who have ischemic cerebral vascular disease, there might be a malfunction in the autoregulation of cerebral vessels or a loss of vascular reserve. In these patients, changes in several parameters such as the cerebral blood volume, oxygen extract fraction and cerebral metabolic rate of oxygen have been reported in PET studies [9–11], suggesting some changes in the mechanism of oxygen supply and metabolism. In single photon emission tomography (SPECT) studies, both decrease in the CBF resting state and impaired increase in CBF under acetazolamide administration have been reported [12, 13]. In severe cases, the steal phenomenon as well as impaired vascular reserve have been observed by acetazolamide-loaded SPECT [14].

Theoretically, there are possibilities that malfunction of vascular autoregulation might affect task-related oxygenation status in ischemic patients. It is expected that this should be clearly revealed by fNIRS imaging which is sensitive to capillary conditions. In this report, we present some cases with severe cerebral ischemia who showed abnormal steal phenomenon and lack of normal hemodynamic response during simple motor tasks in fNIRS imaging.

Materials and Methods

Subjects

We examined 11 right-handed patients (8 males and 3 females, average age: 71.5 ± 6.5 years) with severe cervical internal carotid artery (ICA) stenosis or occlusion who were admitted to our institution for presurgical evaluation. Inclusion criteria for this study were as follows. (1) Severe ICA stenosis of more than 70% based on the NASCET measurements [15] as confirmed by digital subtraction angiography (DSA). (2) Patients showed no motor paresis

on the contralateral side of the affected vessel and were capable of performing the full task as described below. (3) No apparent infarcts were seen in and around the primary sensorimotor cortex (SM1) on MRI. Infarcts were defined as focal lesions of at least 3 mm in diameter, hyperintense on T₂-weighted images. In addition to DSA and MRI, hemodynamic studies including Xenon computed tomography (CT) or SPECT were performed to evaluate the CBF status. All the subjects provided written informed consent for the studies after receiving a full explanation of the study.

Methods

For NIRS imaging measurement, we used a three-wavelength (780, 805 and 830 nm) multi-channel NIRS imaging system (OMM2001, Shimadzu, Japan) which consists of four pairs of emitting and detecting optical fibers. Eight optical fibers were attached to a square pad placed on the affected side of the hemisphere. These optical fibers were arranged with the same interfiber distance, making a grid of 9 detecting points. These points covered a 6×6 cm square area of the scalp surface. The distance between each fiber was 3 cm. The midpoint of each two fibers, at a depth of 1.5–2 cm on the cortical surface was the detecting point [6]. In order to record a specific oxygenation change in and around the SM1 during motor tasks, we set the central detecting channel to the estimated hand area of the SM1, which is just anterior to the central sulcus and 6 cm lateral to the midline measured along the course of the sulcus. The sulcus was determined as the Taylor-Haughton line using surface anatomical landmark [16–18], which is a line between the point 4 cm posterior to the bregma, and cross-point of condylar line and line of sylvian fissure. As interindividual variability of the location of the central sulcus based upon skull landmark is 1.6–2.1 cm [19], the measured area covering 6×6 cm by NIRS probes always includes the hand area of the SM1. Periphery channels surrounding the center did not contain the information of the center of the SM1, because the interprobe distance was 3 cm. In order to confirm that the measured area was located at the designated SM1, MRI was taken in 3 patients with a skin marker, a vitamin E capsule, which was put on the central channel. The sampling time of data acquisition was 130 ms. Changes in oxygenated hemoglobin (HbO₂), deoxygenated hemoglobin (HbR) and total hemoglobin (tHb), were calculated using the differences in the absorption indices at three wavelengths as shown below [20].

$$\text{HbO}_2 = -1.4887 \times \Delta\text{Abs}780 \text{ nm} + 0.5970 \times \Delta\text{Abs}805 \text{ nm} + 1.4847 \times \Delta\text{Abs}830 \text{ nm}$$

$$\text{HbR} = 1.8545 \times \Delta\text{Abs}780 \text{ nm} - 0.2394 \times \Delta\text{Abs}805 \text{ nm} - 1.0947 \times \Delta\text{Abs}830 \text{ nm}$$

$$\text{tHb} = \text{HbO}_2 + \text{HbR} = 0.3658 \times \Delta\text{Abs}780 \text{ nm} + 0.3576 \times \Delta\text{Abs}805 \text{ nm} + 0.39 \times \Delta\text{Abs}830 \text{ nm}$$

Each patient was instructed to close his/her right hand repetitively into a fist at a pace of 1.5 Hz for a period of 10 s, then to rest for 45 s for each trial. All the patients practiced the motor task for more than 5 min before the experiments, so that everyone could perform the task fluently. During the experiment, the same examiner continuously monitored their task performance. Ten consecutive trials were conducted for each subject and time-locked averaging was performed after eliminating trials which contained inappropriate signals such as motion artifacts or incomplete task performance.

Table 1. Clinical characteristics of patients

Case	Age	Sex	Side	Symptom	Stenosis %	VR	tHb decrease in the periphery	HbR in the center
1	69	m	r/l	TIA	77/95	steal	+	increase
2	74	f	r	TIA	85/-	steal	+	n.s.
3	76	m	r	TIA	77/50	decreased	+	n.s.
4	75	m	r	watershed infarct	75/-	steal	-	decrease
5	74	m	r/l	TIA	100/84	decreased	-	n.s.
6	68	m	r	TIA	89/20	decreased	-	increase
7	72	m	r	TIA	90/30	decreased	-	decrease
8	61	m	r/l	asymptomatic	60/100	decreased	-	n.s.
9	74	f	l	TIA	-/86	normal	-	increase
10	65	f	r	asymptomatic	100/-	n.a.	-	n.s.
11	70	m	r	infarction (thalamus)	100/-	n.a.	-	n.s.

Side = Affected side of stenosis; stenosis = degree of carotid artery stenosis under the NASCET measurement (r/l) on DSA; VR = vascular reserve capacity determined from the CBF increase induced by acetazolamide in XeCT or SPECT study; steal = rCBF decrease after acetazolamide loading; decreased = rCBF after acetazolamide loading is 100–120% of resting rCBF; TIA = transient ischemic attack; n.a. = not available; n.s. = statistically nonsignificant change. * $p < 0.01$ (unpaired t test).

We compared the baseline averaged HbO₂/HbR/tHb concentration (in arbitrary unit) for the time period of -5 (prestimulus) to 0 s versus the averaged data for the period of 5–10 s after task initiation in each patient, using the unpaired t test. The significance level was set at $p < 0.01$ in this analysis.

In surgically treated cases, the same measurements were repeated 7–10 days after surgery and serial data were evaluated. The locations of NIRS probes were marked on the scalp using a marker pen, in order to set the probes at the same position in the repeated session. Task performance including pace and force of hand grasping was monitored by the same examiner and confirmed to be same between the preoperative session and the postoperative repeated session.

Results

The clinical information and fNIRS results of all the patients are described in table 1.

Case Descriptions

Case 1

A 69-year-old male, who had a history of reversible ischemic attack of right hemiparesis 6 years before the first study, was referred to our department for preoperative evaluation before carotid artery stenting (CAS) on the left side. On neurological examination, mild left cerebellar ataxia was pointed out and motor weakness was not. Head MRI revealed multiple infarctions in the left cerebellum, bilateral occipital lobe, left temporal lobe and

deep white matter, but no lesion was detected in the left motor cortex (fig. 1a) and the internal capsule. Cerebral angiography showed stenosis of bilateral internal carotid arteries at the cervical bifurcation (right/left = 75%/95% on NASCET measurement; fig. 1b) and left intracranial C4–5 portion of the ICA (fig. 1c). Minute cross-flow through the anterior communicating artery from the right ICA which also had stenosis at the cervical bifurcation was observed (fig. 1d). Vertebral arteries were not examined due to severe stenosis at the origins of these arteries. CBF study revealed mild decreased regional CBF at rest in the left MCA territory (41 ml/100 ml/min) and the steal phenomenon after acetazolamide infusion (33 ml/100 ml/min; fig. 1e).

Functional NIRS during the motor task was performed before the CAS. Figure 2 shows the time course of task-related hemoglobin concentration changes in both the center of the channels and the areas surrounding it, 2–3 cm from the center. In the center of the channels, not only tHb and HbO₂, but also HbR concentration significantly increased during the task (fig. 2a). On the other hand, at one of the surrounding channels, all three parameters decreased during the task synchronously with the center (tHb/HbR decrease: significant, HbO₂: not significant, $p = 0.022$; fig. 2b). Figure 3 shows the topographic image of tHb concentration projected onto the cortical surface constructed from MRI at the time of peak hemoglobin concentration in this patient before intervention.

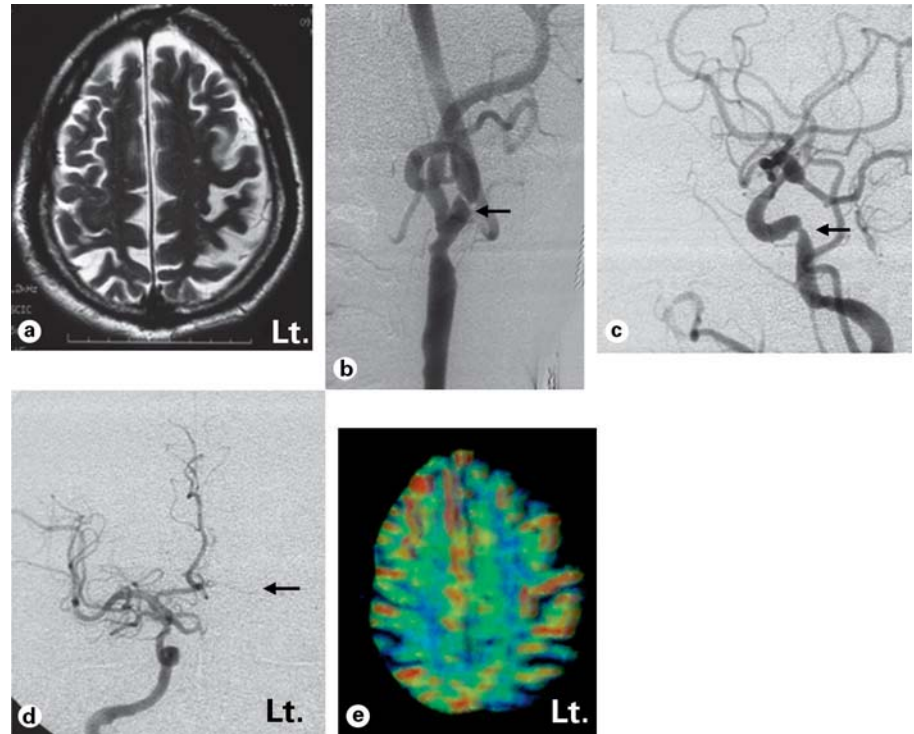


Fig. 1. Pre-operative evaluation of case 1. **a** MRI (T₂WI) which showed no infarction in SM1. **b** DSA of left carotid artery at the cervical bifurcation (lateral view) showing 95% stenosis (arrow) on NASCET measurement. **c** DSA of left intracranial ICA (lateral view), indicating stenosis of C4–5 portion (arrow). **d** DSA of right intracranial ICA (A-P view), showing minute cross-flow through anterior communicating artery to left anterior cerebral artery. **e** Xenon CT after infusion of acetazolamide, showing decreased CBF in left MCA territory.

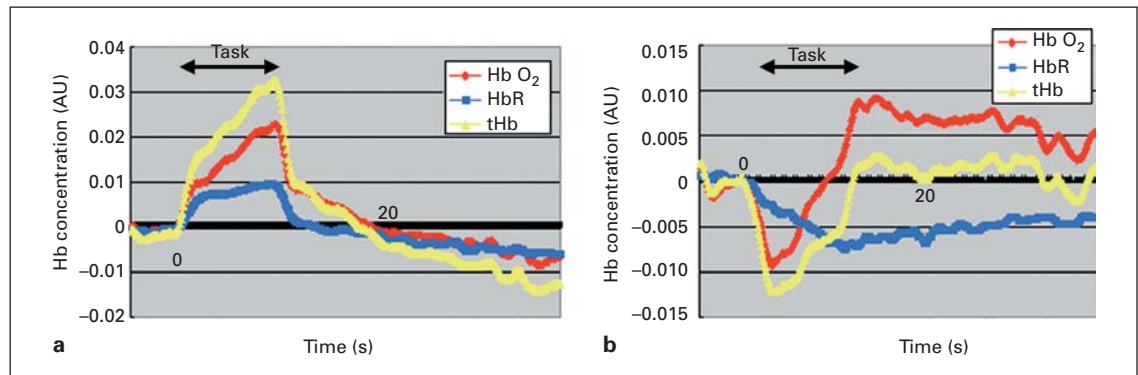


Fig. 2. Time course of relative hemoglobin concentration in case 1. Red, blue and yellow lines indicate change in HbO₂, HbR and tHb concentrations, respectively. **a** Concentration change recorded at the center of SM1. **b** Concentration change recorded in the periphery of SM1. Note that a smoothing algorithm was applied to the data in figures 2–7 for optimal visualization.

An elevated tHb was observed at the center of the primary motor cortex and a decreased tHb was observed around it. CAS was performed with no perioperative irreversible adverse events. At the time of temporary occlusion of the left carotid artery for distal protection of embolus during the intervention, reversible right hemiparesis and consciousness disturbance occurred, imply-

ing poor collateral circulation. Postoperatively, the same measurements were performed. Figure 4 shows the tHb concentration change recorded at the same site as A of figure 3 before and after CAS in this patient. The abnormal decrease during the motor task disappeared after the CAS. Figure 5 shows the HbR concentration change at the center of the channels before and after the CAS. Al-

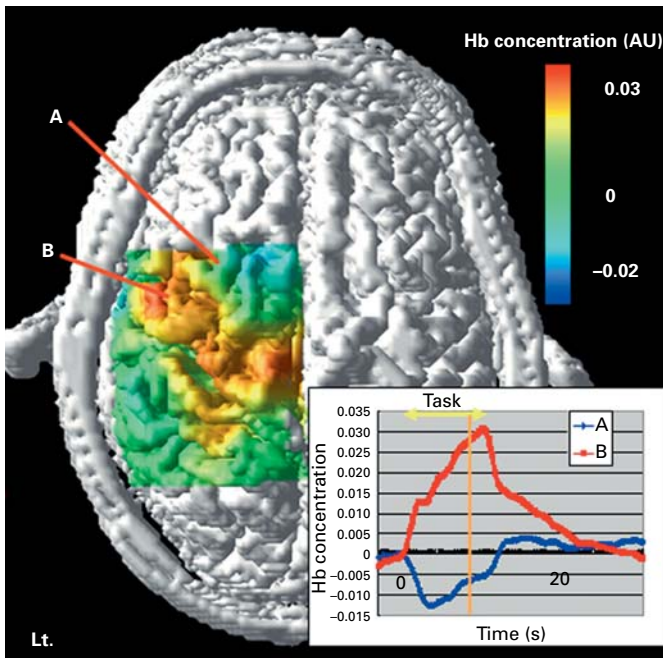


Fig. 3. Topographic image of tHb concentration at peak activation projected onto a 3D cortical surface image reconstructed from MRI data in case 2. The tHb increase is most prominent at the center of SM1 (site B), which is easily discriminated anatomically. A decrease in tHb concentration is observed in the SM1 periphery (site A).

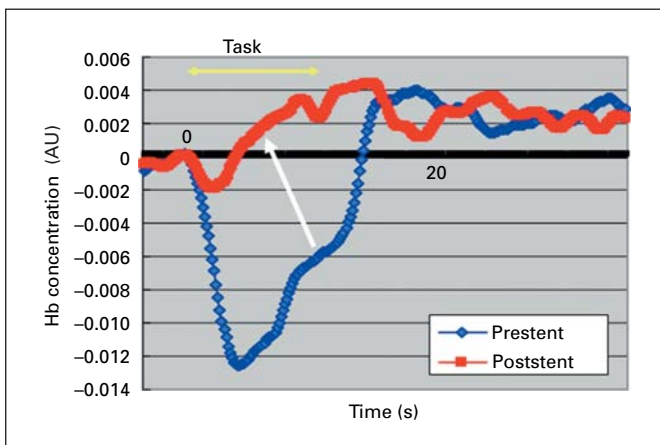


Fig. 4. Comparison of the time course of tHb change during motor task before (blue line) and after (red line) CAS at site A of figure 3. A task-related decrease in tHb was evident before the intervention but disappeared after the stenting.

though task-related decrease in HbR as observed in a normal volunteer has not been restored, marked increase in HbR during the task disappeared.

Case 2

This 74-year-old female was referred to our Department with a complaint of several transient ischemic attacks (left hemiparesis). On admission she showed no neurological deficit. MRI revealed old left thalamic infarction and no other evident infarction (fig. 6a). DSA showed right ICA stenosis (85% on NASCET measurement; fig. 6b) and right middle cerebral artery stenosis (fig. 6c). Blood supply from anterior/posterior communicating artery and external carotid artery into the right MCA territory was poor and cortical anastomosis from posterior cerebral artery into the right MCA territory developed (fig. 6d). CBF study revealed the steal phenomenon after acetazolamide infusion (vascular reserve capacity: -5% in the left MCA territory). Figure 7 shows the results of preoperative fNIRS during the motor task. At the channel inferior to the center, marked task-related decrease in tHb/ HbR was recorded. At the center channel, task-related increase in HbO₂/tHb and task-related decrease in HbR were recorded. After the right carotid endarterectomy, the extent of abnormal decrease in tHb at the inferior channel diminished.

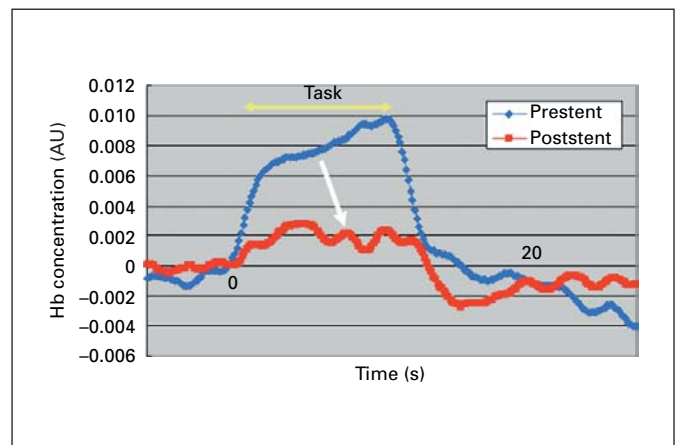


Fig. 5. Comparison of the time course of HbR change during motor task before (blue line) and after (red line) CAS at site B of figure 3. A task-related increase in HbR was evident before the intervention but became indistinct after the stenting.

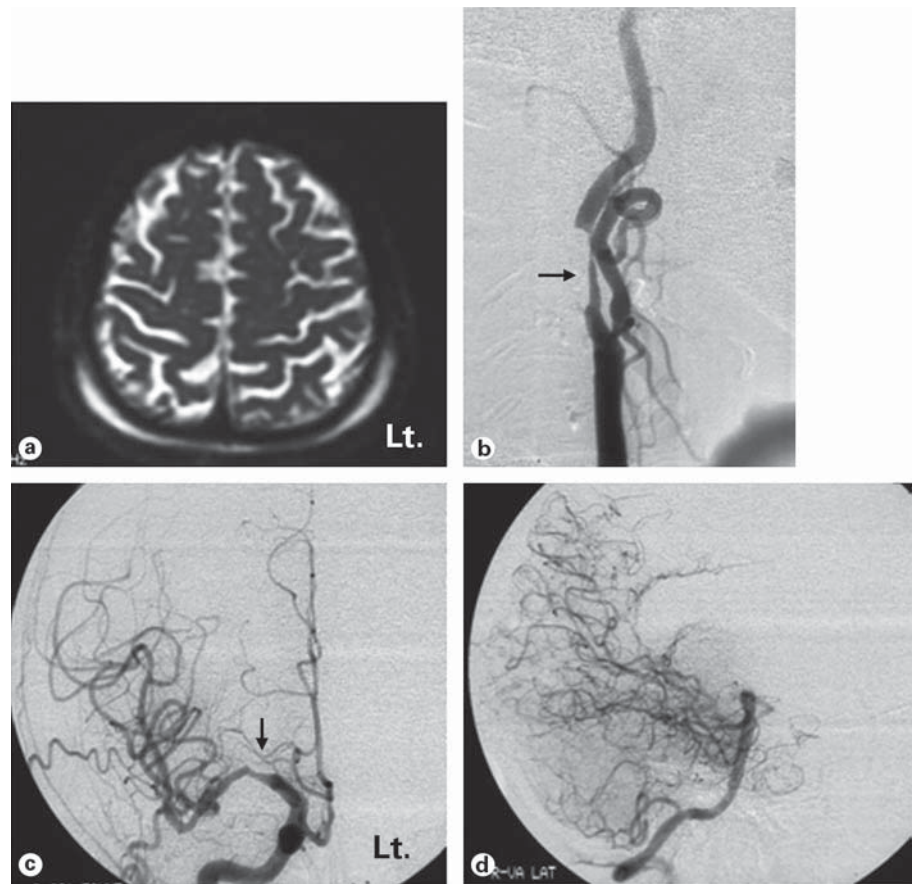


Fig. 6. Pre-operative evaluation of case 2. **a** MRI (T₂WI) which showed no infarction in SM1. **b** DSA of right carotid artery at the cervical bifurcation (lateral view) showing 85% stenosis (arrow) on NASCET measurement. **c** DSA of right intracranial ICA (lateral view), presenting stenosis of right middle cerebral artery (arrow mark). **d** DSA of right vertebral-basilar artery (lateral view), showing cortical anastomosis from posterior cerebral artery into the right MCA territory.

Case 10

This 65-year-old-female was referred to our Department for detailed evaluation after detection of occlusion of central retinal artery and unilateral ICA occlusion. She had no history of ischemic events, MRI showed no infarction and DSA showed rich collateral cross-flow from the contralateral ICA. Neither task-related HbR increase in the center nor tHb decrease in the periphery was shown by fNIRS.

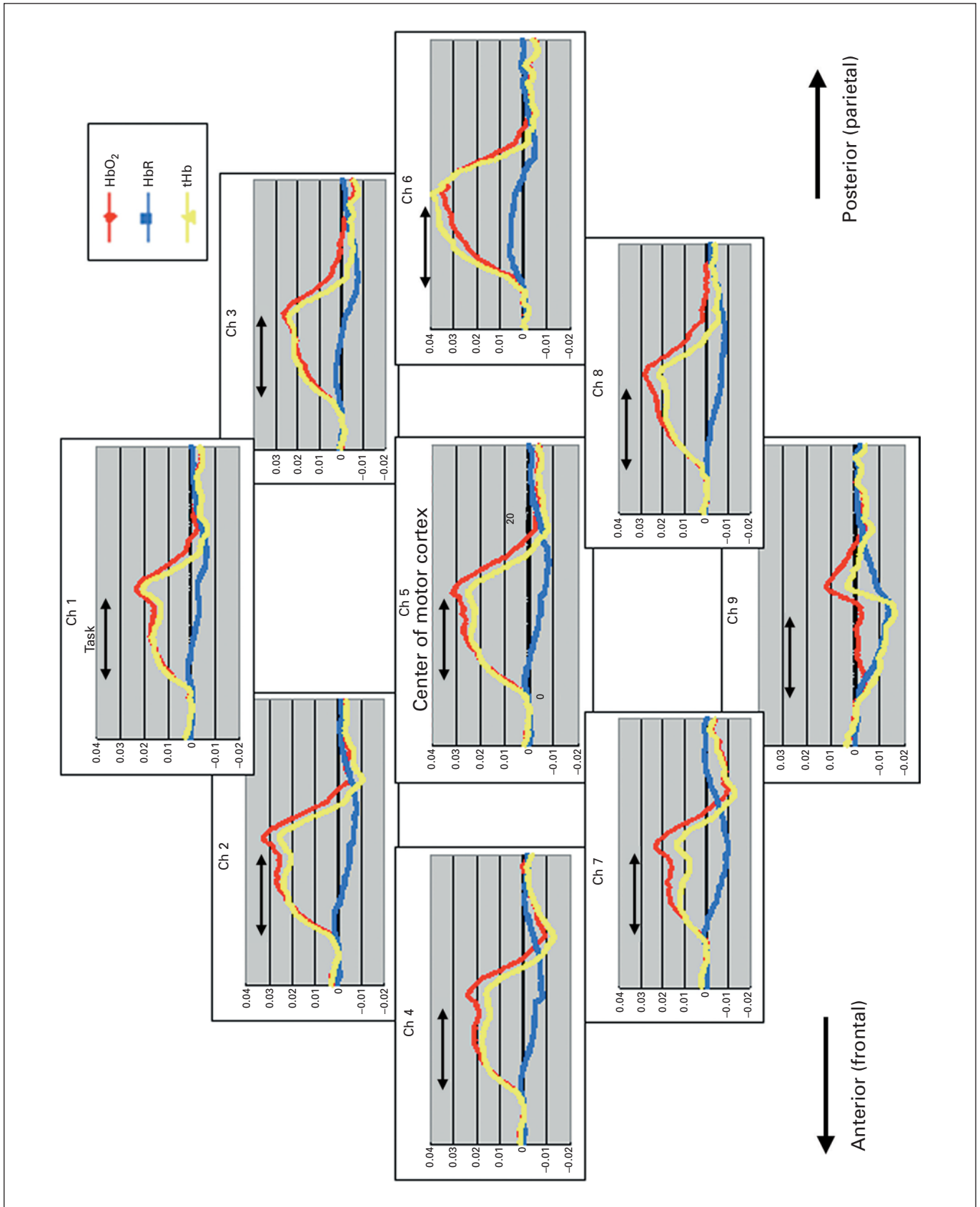
Time Course of HbO₂/tHb Concentration

In all the patients, significant task-related increases in HbO₂ and tHb concentration were observed at the center channels. Eight out of 11 patients showed HbO₂ and tHb increase in all recorded channels similar to data from healthy volunteers (data not shown [21, 22]). However, in other 3 patients (cases 1–3), a significant task-related decrease in tHb concentration was observed in the channel just anterior or inferior to the central channel, which showed a robust increase in tHb concentration. Figure 8 shows the change in tHb concentration measured at the

center and the periphery of the SM1 of case 2. The tHb concentration in the periphery of the SM1 decreased simultaneously with motor task initiation and returned to its baseline soon after task termination. This decrease in tHb concentration was a synchronous mirror of the positive value activation detected in the center of the SM1 area. In these 3 patients, changes in task-related HbO₂ concentration varied. Case 1 showed significant decrease, cases 2 and 3 showed nonsignificant change.

All of these 3 cases were surgically treated (case 1: CAS; cases 2 and 3: carotid endarterectomy). The peripheral decrease in tHb during motor tasks disappeared completely in case 3, and partial recovery was seen in cases 1 and 2 as shown in case descriptions.

Fig. 7. Time course of hemoglobin concentration change in and around the primary motor cortex. ch5 is located at the center of SM1, where task-related increase in HbO₂ and tHb and task-related decrease in HbR were recorded. In ch9, which is located inferior to ch5, task-related decrease in tHb was recorded. x-axis = Time (s); y-axis = concentration (AU).



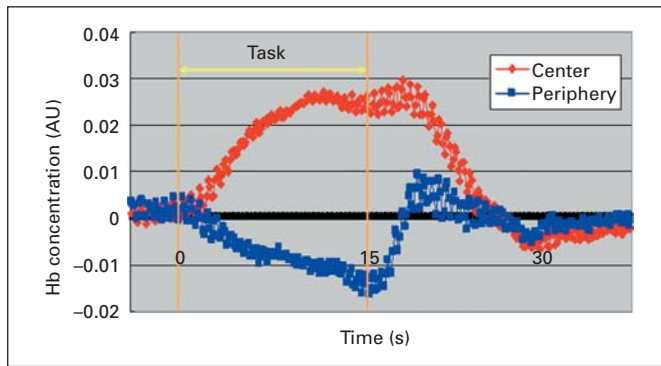


Fig. 8. Time course of the relative concentration change of tHb recorded at the center and the periphery of SM1 in case 2. The red line indicates the tHb change recorded at the center of SM1, indicating a robust increase in tHb during motor task. The blue line indicates the marked task-related decrease in tHb in the area adjacent to SM1.

Although the correlation between insufficiency of vascular reserve and tHb decrease at the periphery of the SM1 or HbR increase at the center of the SM1 cannot be calculated due to the limited number of cases, 2 patients who showed the steal phenomenon in the CBF study using acetazolamide also showed tHb decrease in the periphery of the SM1.

Time Course of HbR Concentration

Significant decrease in HbR at the center of the detected channels, which is reported to be a typical change in normal subjects [21, 23], was only observed in 2 out of 11 patients. However, significant increase in HbR was observed in 3 cases (cases 2, 6 and 9). Carotid endarterectomy was performed in cases 2 and 6; partial recovery was seen in case 2 (fig. 5), but task-related increase in HbR was still seen in case 6 at the same channel of this patient.

Discussion

Functional NIRS can present us information about cortical hemodynamics and oxygenation status during functional activity through three parameters (HbO₂, HbR and tHb). The ratio of these three concentrations is supposed to be determined by a combination of oxygen consumption, supply of oxygenated arterial blood flow and drainage of deoxygenated venous blood. Thus, a variety of results regarding the concentration of these three pa-

rameters can be expected in patients with chronic ischemia and lacking adequate autoregulation. In studies using normal volunteers, a combination of increase in HbO₂ and tHb and synchronous decrease in HbR 3 s after motor stimulation in the activation center has been reported as a typical change [21, 22, 24]. From here, we will discuss the abnormal results obtained in this study from the points of cortical oxygen consumption and disturbed blood supply. Specifically we will focus on tHb decrease in the periphery and HbR increase in the center of the SM1.

tHb Decrease in the Periphery of the SM1

In functional neuroimaging studies utilizing hemodynamic response to stimulation, a decrease in the CBF has seldom been considered. Recently, a negative BOLD response indicating cortical CBF decrease has been reported during visual stimulation in young children under fMRI/PET study [25, 26]. In NIRS studies, CBF decrease was recorded during epilepsy [27] and verbal tasks [28]. However, among numerous fNIRS studies, no task-related decrease in tHb which correlates with rCBF [29] during the motor task has been reported to date [22, 30].

We observed, in a few cases, the coexistence of task-related increase and decrease in cortical tHb concentration during a motor task. As these events occur synchronously with each other, this phenomenon is indirectly indicative of a distributional change in the rCBF. In other words, a certain volume of blood is stolen from the periphery of the SM1 to its center. This phenomenon implies that normal physiological mechanisms that induce CBF increase in and around the functional cortex during functional activation are dysfunctional in these subjects. When the rCBF demand requires fulfillment in patients with severe impairment in autoregulation due to severe ICA stenosis with poor collateral circulation, the rCBF supply into the center of the functional cortex is managed by depriving the neighboring cortex of blood. The results observed in the present study, where the decrease in tHb during the motor task partially disappeared after surgery, indicate that this phenomenon is attributable to cerebral ischemia. All the patients who showed this abnormal response had a history of hemodynamic ischemic events, showed impaired reserve capacity, including the steal phenomenon under the administration of acetazolamide in CBF studies and poor filling from the ipsilateral ICA into the MCA territory in the intracranial angiography being dependent upon blood from other vessels. This clinical information supports that this motor-related intra-

cortical steal phenomenon might imply the degree of severity of the hemodynamic compromise in the SM1. We cannot statistically differentiate between patients who showed this steal phenomenon during motor tasks and those patients who did not based on our data alone due to the limited number of cases. However, the fact that 2 out of 3 patients who showed the steal phenomenon in a conventional CBF study using acetazolamide also showed a tHb decrease in fNIRS imaging during motor tasks might be indicative of a correlation between these two methodologies. As the steal phenomenon in a CBF study using acetazolamide is reported to be related to poor prognosis [31, 32], these motor-related intracortical steal phenomena might also be a predictive factor of poor prognosis. We assume that any induction of blood vessel dilatation, either by chemical agents or by physiological stimulation, would be impaired in patients with dysfunctional autoregulation, although further investigation will be required to elucidate the relationship between the two. The reason why one case (case 4) who showed the steal phenomenon in a conventional CBF study lacked a decrease in tHb in fNIRS might be afforded by elucidation of the difference between drug-induced and stimulation-induced dilatation of vessels. If physiological stimulation induces fewer and more localized dilatation of blood vessels than chemical agents do, the steal phenomenon in both CBF and fNIRS studies would show severer ischemic status than in CBF study alone. The fact that cases 1 and 2 had tandem stenotic lesions (cervical ICA + intracranial ICA or MCA) and case 4 did not (unilateral carotid artery stenosis only) implies that the former two had severer conditions, leading to tHb decrease in fNIRS study.

HbR Increase in the Center of the SM1

It is widely accepted that task-related cortical oxygenation induces HbR decrease in the activated cortex in optical studies [33] and fNIRS studies [21, 22, 34]. The common explanation for the HbR decrease in normal subjects is based upon a PET study revealing the stimulus-induced focal augmentation of cerebral blood flow (mean: 29%) far exceeded the concomitant local increase in the tissue metabolic rate (mean: 5%) [2]. This concept is also used for the BOLD signal mechanism [35] in fMRI studies. However, we recorded abnormal significant increase in HbR concentration during motor task at the center of the channels in 3 cases. On the other hand, HbR decrease was recorded in only 2 out of 11 cases. As compared to 90% detection rate of HbR decrease in normal healthy adults (data not shown), the rate we obtained

from this study was extraordinarily low. Murata et al. [36] reported that in ischemic patients, task-related HbR increase can sometimes be seen in fNIRS study, with which our data coincide. Partial recovery from abnormal HbR increase after surgery in these patients suggests that this abnormal result is also related to cortical ischemia and can be modulated by alteration of cortical hemodynamics.

In case 1 who showed the severest steal in conventional CBF study, both abnormal tHb decrease in the periphery and abnormal HbR increase in the center were recorded. However, in other cases, these two abnormal events did not coincide. Moreover, in case 4 who showed the steal phenomenon in a conventional CBF study, neither any abnormality in tHb change, nor task-related HbR increase in fNIRS was shown. Thus, the correlation of tHb decrease in the periphery and HbR increase in the center cannot be made clear from this study. The fact that one of the patients who showed HbR increase in the center had a normal vascular reserve in conventional CBF study might imply that this change may be related to a less severe ischemic status. Lack of complete coexistence of these two abnormal results suggests that these changes are induced through different mechanisms, although both are related to cortical ischemia. A further study will be required to elucidate which mechanisms underlie these changes, what differences lie between them and which is more predictive of clinical prognosis.

Conclusion

We have successfully recorded abnormal hemodynamics during motor tasks in patients with compromised cerebral circulation and their recovery after surgery in this fNIRS study. This is the first report on the intracortical steal phenomenon (tHb decrease in the periphery of the SM1) during simple hand movement tasks in patients with severe cerebral ischemia. Additional results confirmed previous reports on HbR increase in the center of the SM1. We believe this motor-related steal phenomenon is extremely informative as it specifically indicates abnormal vascular autoregulation and possibly poor outcome. Noninvasive fNIRS imaging can provide us with useful information on abnormal cortical hemodynamics, and its repeated measurements might be potentially valuable for following the clinical course of ischemia and for evaluating treatment outcome.

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