Bedside Monitoring of Cerebral Blood Oxygenation and Hemodynamics after Aneurysmal Subarachnoid Hemorrhage by Quantitative Time-Resolved Near-Infrared Spectroscopy

Noriaki Yokose[1], Kaoru Sakatani[1,2,3], Yoshihiro Murata[1], Takayuki Awano[1], Takahiro Igarashi[1], Sin Nakamura[1], Tatsuya Hoshino[1], Yoichi Katayama[1,3]

Key words
- Cerebral ischemia
- Near-infrared spectroscopy
- Oxygen metabolism
- Transcranial Doppler sonography
- Vasospasm

Abbreviations and Acronyms
CBO: Cerebral blood oxygenation
CBV: Cerebral blood volume
$CoSO_2$: Cortical oxygen saturation
CT: Computed tomography
CW: Continuous wave
deoxy-Hb: Deoxyhemoglobin
DSA: Digital subtraction angiography
FD-NIRS: Frequency domain NIRS
Hb: Hemoglobin
MCA: Middle cerebral artery
MRI: Magnetic resonance imaging
NIRS: Near-infrared spectroscopy
oxy-Hb: Oxyhemoglobin
PET: Positron emission tomography
SAH: Subarachnoid hemorrhage
SjO_2: Jugular venous oxygen saturation
TCD: Transcranial Doppler sonography
t-Hb: Total hemoglobin
TR-NIRS: Time-resolved near-infrared spectroscopy
WFNS: World Federation of Neurosurgical Society

From the [1]Department of Neurological Surgery, [2]Division of Optical Brain Engineering, [3]Division of Applied System Neuroscience, Nihon University School of Medicine, Tokyo, Japan.

To whom correspondence should be addressed: Kaoru Sakatani, M.D., D.M.Sc., Ph.D. [E-mail: sakatani@med.nihon-u.ac.jp].

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BACKGROUND: **Early detection of vasospasm is essential for the treatment of delayed ischemic neurological deficits in subarachnoid hemorrhage (SAH). We evaluated cerebral blood oxygenation (CBO) changes after SAH employing quantitative time-resolved near-infrared spectroscopy (TR-NIRS) for this purpose.**

METHODS: **We investigated 11 age-matched controls and 14 aneurysmal SAH patients, including 10 patients with WFNS grade V and 4 patients with grade II. Employing TR-NIRS, we measured the cortical oxygen saturation ($CoSO_2$) and baseline hemoglobin concentrations in the middle cerebral artery territory. Measurements of TR-NIRS and transcranial Doppler sonography (TCD) were performed repeatedly after SAH.**

RESULTS: **In six patients, the $CoSO_2$ and hemoglobin concentrations remained stable after SAH; digital subtraction angiography (DSA) did not reveal vasospasm in these patients. In eight patients, however, $CoSO_2$ and total hemoglobin decreased abruptly between 5 and 9 days after SAH. DSA revealed diffuse vasospasms in six of eight patients. The reduction of $CoSO_2$ predicted occurrence of vasospasm at a cutoff value of 3.9%-6.4% with 100% of sensitivity and 85.7% of specificity. TCD failed to detect the vasospasm in four cases, which TR-NIRS could detect. Finally, TR-NIRS performed on Day 1 after SAH revealed significantly higher $CoSO_2$ than that of controls ($p = .048$), but there was no significant difference in total hemoglobin.**

CONCLUSION: **TR-NIRS detected vasospasm by evaluating the CBO in the cortex and may be more sensitive than TCD, which assesses the blood flow velocity in the M1 portion. The cerebral oxygen metabolism in SAH might be reduced by brain damage due to aneurysmal rupture.**

INTRODUCTION

Arterial vasospasm is the most common cause of delayed ischemic neurological deficits in patients with aneurysmal subarachnoid hemorrhage (SAH) (31). Transcranial Doppler sonography (TCD) has been used to detect vasospasms after SAH (8, 10, 19), but its sensitivity is not high (1, 8, 17, 30). In addition, TCD does not provide information about the cerebral circulation and oxygenation in the cortex. A simple noninvasive method for bedside assessments of cerebral ischemic status is still required.

Near-infrared spectroscopy (NIRS) appears to be an attractive alternative method, since it can measure concentration changes of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) in the cortical vessels (15, 28). Various studies have shown the usefulness of NIRS for detecting cerebral ischemia during carotid endarterectomy (2, 3); however, it is difficult to apply NIRS to the diagnosis of vasospasm after SAH, since commercially available NIRS, which uses continuous-wave (CW) light, does not provide quantitative values of the baseline Hb concentrations (15, 28). In contrast to CW-NIRS, time-resolved near-infrared spectroscopy (TR-NIRS) (7) and frequency-domain near-infrared spectroscopy (FD-NIRS) (5, 9) permit quantitative measurement of the Hb concentrations; TR-NIRS uses picosecond light pulses (26), whereas FD-NIRS employs intensity-modulated light at more than 100 MHz (5, 9).

Recently, we demonstrated significant correlations between the Hb concentrations in

the cortex measured by TR-NIRS and Positron emission tomography (PET) in normal adults during acetazolamide administration (23). TR-NIRS has been used for functional studies on normal adults (12, 27, 29) and for evaluation of the cerebral circulation in stroke patients (18) and newborn infants (14). In this study, we examined whether TR-NIRS can detect cerebral ischemia caused by vasospasm in patients with aneurysmal SAH. Initially, we measured normal values for the cortical oxygen saturation ($CoSO_2$) and Hb concentrations in normal adults. We then repeatedly measured the $CoSO_2$ and Hb concentrations in patients after the onset of SAH, and these data were compared with the results of TCD.

MATERIALS AND METHODS

Patients Characteristics

We investigated 14 patients with aneurismal SAH (six males, eight females; mean age [± SD] = 63 ± 11.0 years) and 11 age-matched controls (five males, six females; mean age [± SD] = 60.6 ± 15.2 years; $p > .05$). In all patients, SAH wa7› Tj/T111
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Table 2. Comparison of $CoSO_2$ and Hb Concentrations in Age-Matched Controls and SAH Patients on Day 1 after SAH

	oxy-Hb (μM)	deoxy-Hb (μM)	t-Hb (μM)	$CoSO_2$ (%)
Age-matched controls	42.0 ± 6.4	38.7 ± 5.6	67.4 ± 8.2	68.0 ± 1.4
SAH patients	50.5 ± 5.1	15.9 ± 1.6[a]	66.4 ± 5.5	75.2 ± 2.3[b]

Note: Averaged values are expressed as mean ± SE. CoSO2, cortical oxygen saturation; Hb, hemoglobin; SAH, subarachnoid hemorrhage; oxy-Hb, oxyhemoglobin; deoxy-Hb, deoxyhemoglobin; t-Hb, total hemoglobin.
[a] $P = .002$.
[b] $P = .048$, compared with the age-matched controls and SAH patients.

profiles were fitted into the photon diffusion equation (26) using the nonlinear least square fitting method. The reduced scattering and absorption coefficients for the three wavelengths were calculated. The concentrations of oxy-Hb, deoxy-Hb, total Hb (=oxy-Hb + deoxy-Hb; t-Hb), and $CoSO_2$ were then calculated using the least squares method. The concentrations of Hb were expressed in micromoles.

We measured mainly the $CoSO_2$ and Hb concentrations in the middle cerebral artery (MCA) territory of the temporal lobe, because these areas are commonly affected by vasospasm after SAH. The position of the probe was displayed on the anatomical magnetic resonance imaging (MRI) of each subject by a frameless stereotaxic system (Brainsight; Rogue Research, Montreal, Canada), which has been used in transcranial magnetic stimulation (11). The system consists of a position sensor, which uses infrared light, trackers (an array of three reflective spheres), and a personal computer; we constructed a special attachment for fixing the tracker on the optodes (**Figure 1B**). TR-NIRS measurements were performed repeatedly for 14 days after the onset of SAH.

TCD Measurements in the Patients

The blood flow velocity in the MCA (M1 portion) was measured by TCD (EME Transcranial Doppler System; Nicolet Biomedical Inc., WI, USA); a 2-MHz pulsed Doppler probe was used via the transtemporal window. TCD measurements were performed repeatedly by the same investigator (SN) for 14 days after SAH. Occurrence of vasospasm was considered to take place when the mean flow velocity was greater than 120 cm/s (1).

Postoperative DSA

We performed DSA to confirm occurrence of vasospasm in all patients. The DSA was performed 7 days after SAH or when TR-NIRS or TCD indicated occurrence of vasospasm; we adopted decreases of $CoSO_2$ by 5% for tentative criterion of occurrence of vasospasm at the time of experiments.

Data Analysis

We evaluated differences in cerebral perfusion and oxygen metabolism between SAH patients and controls; the $CoSO_2$ and hemoglobin (Hb) concentrations in the patients on Day 1 after SAH were compared with those of the controls using the Mann–Whitney U test. In addition, we evaluated the effect of vasospasm on cerebral perfusion and oxygen metabolism by comparing the $CoSO_2$ and Hb concentrations before and after vasospasm in the patients with vasospasm using the Wilcoxon t test.

RESULTS

Table 2 compares the mean value of $CoSO_2$ and concentrations of oxy-Hb, deoxy-HB, and total hemoglobin (t-Hb) in the SAH patients and age-matched controls. In the SAH patients, TR-NIRS measurements on day 1 after SAH demonstrated significantly lower concentrations of deoxy-Hb ($p = .002$) and higher $CoSO_2$ ($p = .048$) compared with those of the controls. However, there were no significant differences in oxy-Hb ($p > .05$) and t-Hb ($p > .05$) between the patients and controls.

Repeated measurements of TR-NIRS after SAH demonstrated only small changes in $CoSO_2$ (<5%) in six patients. These patients included one case with WFNS grade II and five cases with grade V. DSA performed at 7 days after SAH did not reveal cerebral vasospasm in the patients. **Figure 2** showed the mean values of $CoSO_2$ and concentrations of t-Hb in the patients during the course of TR-NIRS measurements.

In contrast, eight patients showed decreases in $CoSO_2$ by more than 5% reduction between 5 and 9 days after SAH; the patients included three cases with WFNS grade II and five cases with grade V. The DSA performed on the same day demonstrated no apparent vasospasm in two pa-

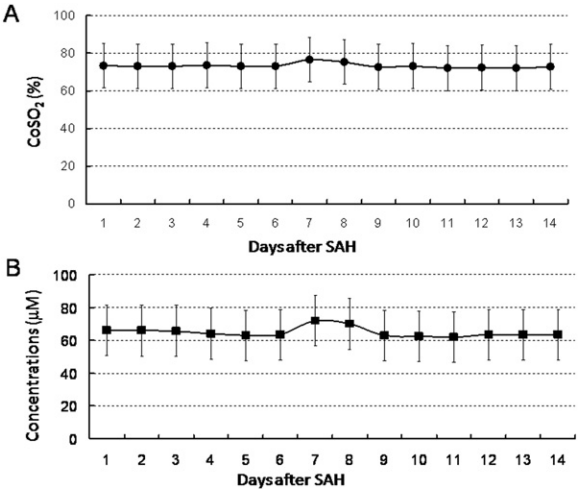

Figure 2. Chronological changes of cortical oxygen saturation ($CoSO_2$) (**A**) and total hemoglobin (**B**) in the middle cerebral artery territory of subarachnoid hemorrhage (SAH) patients without vasospasms. The ordinates in **A** and **B** indicate the oxygen saturation (%) and hemoglobin concentrations (μM), respectively. The abscissae indicate the number of days after SAH.

Figure 3. A, Chronological changes of $CoSO_2$ measured by TR-NIRS and blood flow velocity measured by transcranial Doppler sonography in an SAH patient with vasospasm (patient No. 2). The solid line indicates changes of $CoSO_2$, whereas the dotted line indicates changes of blood flow velocity. The ordinates on the left and right sides indicate the oxygen saturation (%) and blood flow velocity (cm/s), respectively. The abscissa indicates the number of days after SAH. **B,** Cerebral angiography before (left) and after (right) intraarterial injection of fasudil hydrochloride. Note that the vasospasm was relieved by intraarterial injection of fasudil hydrochloride.

tients with WFNS grade II; they did not show neurological symptom at that time. However, five patients with WFNS grade V and one patient with WFNS grade II exhibited severe vasospasms extending to the peripheral MCA. **Figure 3** represents an example (patient No. 2) of the chronological changes in $CoSO_2$ measured by TR-NIRS and blood flow velocity measured by TCD. TR-NIRS showed abrupt decreases of $CoSO_2$ at 5 days after SAH. Intraarterial injection of fasudil hydrochloride (30 mg) relieved the vasospasm and increased the $CoSO_2$ to the previous levels. TCD, however, did not demonstrate an acceleration of blood flow velocity indicative of vasospasm in four of six patients including this patient.

To evaluate the effect of vasospasm on cerebral perfusion and oxygen metabolism, we compared the $CoSO_2$ and Hb concentrations before and after vasospasm in the patients with vasospasm. We found significant decreases of $CoSO_2$ ($p = .027$), t-Hb ($p = .027$), and oxy-Hb ($p = .027$), after vasospasm, indicating that vasospasm caused ischemic changes in the cortex (**Table 3**).

DISCUSSION

The present study represents the first application of TR-NIRS to detection of vasospasm in patients with SAH. Prior to this study, we have assessed the reliability of TR-NIRS measurements by undertaking simultaneous measurements of TR-NIRS and PET in normal adults (23). We revealed significant correlations between the changes in TR-NIRS–measured cerebral blood volume (CBV) and PET-measured CBV in the corresponding cortical region during acetazolamide administration at optode separations of 2-5 cm. These findings indicate that the present TR-NIRS measurements (3-cm optode distance) reflected the Hb concentrations in the cortex, although the Hb concentration in the cortex could not be measured selectively by TR-NIRS (see discussion below).

By means of TR-NIRS, we were able to detect the occurrence of vasospasm in patients with angiographical vasospasm. TR-NIRS demonstrated decreases of $CoSO_2$, t-Hb, and oxy-Hb during vasospasm, indicating that vasospasm caused cortical ischemia. We estimated the cutoff values of 3.9%-6.4% reduction in $CoSO_2$, which predict occurrence of vasospasm with high sensitivity (100%) and specificity (85.7%). Interestingly, TCD failed to detect vasospasm in four of six cases in which TR-NIRS could detect occurrence of vasospasm. It should be noted that TR-NIRS detects vasospasm by evaluating the ischemic status in the cortex caused by vasospasms and can therefore detect vasospasms regardless of the affected artery insofar as vasospasm causes cortical ischemia, which decreases the $CoSO_2$ and t-Hb. In contrast, TCD could fail to detect vasospasms extending to the peripheral MCA because narrowing of the peripheral MCA increases the vascular re-

Table 3. Comparison of $CoSO_2$ and Hb Concentrations before and after Cerebral Vasospasm in SAH Patients

	oxy-Hb (μM)	deoxy-Hb (μM)	t-Hb (μM)	$CoSO_2$ (%)
Before vasospasm	51.7 ± 10.6	18.5 ± 4.4	70.3 ± 14.7	73.9 ± 1.8
After vasospasm	32.7 ± 4.8[a]	19.1 ± 3.8	51.8 ± 8.4[b]	64.1 ± 2.5[c]

Note: Averaged values are expressed as mean ± SE.
[a] $P = .0025$.
[b] $P = .0038$.
[c] $P = .007$, compared with before vasospasm.

sistance, which tends to suppress the acceleration of blood flow in the M1 segment (25). Indeed, DSA revealed diffuse vasospasm in the cases where TCD failed to detect an acceleration of blood flow velocity indicative of vasospasm. Our results suggest that TR-NIRS is more sensitive than TCD for detecting vasospasms after SAH. In addition, TR-NIRS measurement of cerebral blood oxygenation is simple and easy compared to TCD, which requires technical skill for precise measurement of blood flow velocity. However, it should be noted that this was a pilot study in which the numbers of subjects and vessels evaluated with TCD were limited. Further study is necessary to evaluate fully the usefulness of TCD and TR-

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