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Evaluation of cerebral ischemia using near-infrared spectroscopy with oxygen inhalation

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Abstract. Conventional methods presently used to evaluate cerebral hemodynamics are invasive, require physical restraint, and employ equipment that is not easily transportable. Therefore, it is difficult to take repeated measurements at the patient's bedside. An alternative method to evaluate cerebral hemodynamics was developed using near-infrared spectroscopy (NIRS) with oxygen inhalation. The bilateral fronto-temporal areas of 30 normal volunteers and 33 patients with cerebral ischemia were evaluated with the NIRS system. The subjects inhaled oxygen through a mask for 2 min at a flow rate of 8 L/min. Principal component analysis (PCA) was applied to the data, and a topogram was drawn using the calculated weights. NIRS findings were compared with those of single-photon-emission computed tomography (SPECT). In normal volunteers, no laterality of the PCA weights was observed in 25 of 30 cases (83%). In patients with cerebral ischemia, PCA weights in ischemic regions were lower than in normal regions. In 28 of 33 patients (85%) with cerebral ischemia, NIRS findings agreed with those of SPECT. The results suggest that transmission of the changes in systemic SpO_2 were attenuated in ischemic regions. The method discussed here should be clinically useful because it can be used to measure cerebral ischemia easily, repeatedly, and noninvasively. [DOI: 10.1117/1.JBO.17.9.096002]

Keywords: near-infrared spectroscopy; cerebral ischemia; oxygen inhalation; principal component analysis.

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1 Introduction

The number of patients with cerebral ischemia has been increasing recently, and this condition has become an important public health issue. Therefore, diagnosis and medical treatment for it are becoming increasingly important. Evaluation of cerebral perfusion is useful in patients with cerebral ischemia. Conventional methods for evaluation of cerebral hemodynamics currently include angiography, perfusion computed tomography (CT), perfusion magnetic resonance imaging (MRI), transcranial Doppler (TCD), single-photon-emission computed tomography (SPECT), and positron emission tomography (PET). These techniques allow the measurement of cerebral perfusion deficits, but they have several drawbacks. Angiography is invasive, perfusion CT and MRI require injection of a contrast agent, and SPECT and PET require administration of a radioisotope. TCD and arterial spin labeling MRI have been developed as noninvasive, *in vivo* imaging methods. However, with TCD, the measurement area is limited and the accuracy of the examination depends on the skill of the operator. Arterial spin labeling MRI is still insufficient with regard to diagnostic accuracy. All the aforementioned methods require that the patient be restrained, which makes repeated measurements difficult.[1–4] Furthermore, measurements at the bedside cannot be acquired because the equipment required for these examinations (other than TCD) are not easily transportable.

On the other hand, near-infrared spectroscopy (NIRS) can continuously measure real-time changes in the concentration of oxygenated hemoglobin (HbOxy), deoxygenated hemoglobin (HbR), and total hemoglobin (HbTotal) in the cerebral tissues.[5–7] HbTotal is defined as the sum of HbOxy and HbR. The basis of this approach is the modified Beer-Lambert law. This method is suitable for repeated measurement of changes in cerebral oxygenation at the patient's bedside. Compared to other modalities, it is simple, noninvasive, requires minimal patient restraint, has high temporal resolution, and is transportable.[8,9] Optical topography (OT) is a NIRS technique that provides spatial maps of hemodynamic and oxygenation changes.[10] OT has been increasingly used in recent years in various clinical fields, including neurosurgery, neurology, and psychiatry.[11–13]

This report proposes a method for measuring cerebral oxygenation using OT with oxygen inhalation. This technique can be used to evaluate cerebral ischemia easily and repeatedly in real time and can be used to complement conventional methods.[14–16]

2 Subjects

A total of 30 normal volunteers without a history of cerebral disease or risk factors of stroke (25 men, 5 women; age range, 22 to 56 years) and 33 patients with cerebral ischemia in whom the decrease in cerebral blood flow (CBF) in the area of the middle cerebral artery (MCA) was studied with N-isopropyl-p-[^{123}I] Iodoamphetamine (^{123}I-IMP) SPECT (29 men, 4 women; age range, 58 to 78 years). Cases of stenosis or occlusion of the internal carotid artery (ICA) or MCA were visualized with MR angiography, and cerebral infarctions were not observed in any cases in the cerebral cortex in the area of the MCA. In patients with cerebral ischemia, the average

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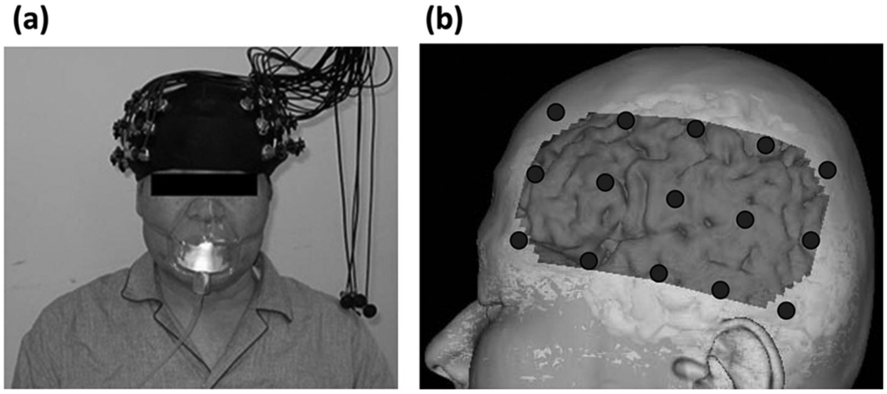

Fig. 1 Configuration of probes. (a) Two faces of 3×5 probe arrays were set on the scalp symmetrically, and the oxygen face mask was placed on the subject. (b) Probes covered the bilateral fronto-temporal areas in order to measure the area of the MCA.

duration from the time the vascular lesions were found by MR angiography to the OT measurement was 5.6 months. The lesions included 24 ICA stenoses, 4 ICA occlusions, 3 MCA stenoses, and 2 MCA occlusions.

This study was approved by the Ethics Committee of Jichi Medical University, and informed consent was obtained from all subjects.

3 Materials and Methods

3.1 *Methods of Measurement for OT*

Measurements were performed on a continuous-wave OT system (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan) with 48 channels using two faces of 3×5 probe arrays. In this system, near-infrared light rays with wavelengths of 695 and 830 nm were guided by optical fiber bundles and transmitted into the cranium. Reflections of the near-infrared rays were detected in receiving probes set on the scalp 30 mm away from the transmitting probes. Near-infrared light is absorbed by hemoglobin in the extracerebral and cerebral tissues. Therefore, OT signals are influenced by both scalp and cerebral hemodynamics. However, previous studies have shown that changes in cerebral hemodynamics and oxygenation due to manipulation of breathing gas can be detected in settings similar to those in the present study.[17–19] In order to measure changes in concentrations of hemoglobin in the area of the MCA, probes were symmetrically set on the subject's scalp to cover the bilateral fronto-temporal areas. Measurement was performed with a response rate of 10 Hz.

An oxygen face mask (OX-135, Atom Medical Corporation, Tokyo, Japan) was placed on the subject as shown in Fig. 1, and peripheral oxygen saturation (SpO_2) was measured at the tip of the subject's index finger using a SpO_2 monitor (OLV 3100, Nihon Kohden Corporation, Tokyo, Japan). Air was delivered through the oxygen face mask at a flow rate of 8 L/ min, and OT measurement was started. After OT data were stabilized, the air was switched to oxygen at the same flow rate for a period of 2 min, and then it was switched back to air at the same flow rate. The changes in SpO_2 showed a trapezoidal pattern with this manipulation. Changes in HbOxy associated with oxygen inhalation in the cerebral tissues were measured using OT. The subjects continued breathing in a free and relaxed manner during the measurement in order to minimize the influence of physiological factors that could cause changes in cerebral blood volume (CBV).[20]

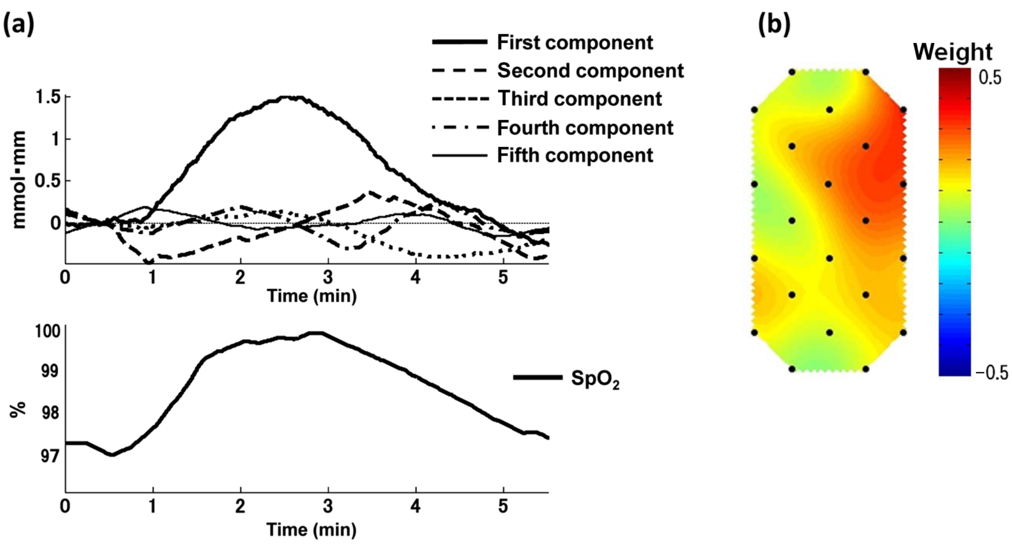

Fig. 2 Analysis of measured data (a) Principal component analysis of the data. In the upper graph, the principal components are shown from the first component to the fifth component. The change in SpO_2 is shown in the lower graph. Correlation coefficients of each component and SpO_2 were calculated. (b) Topogram drawn using the weights of the component which had the highest correlation coefficient.

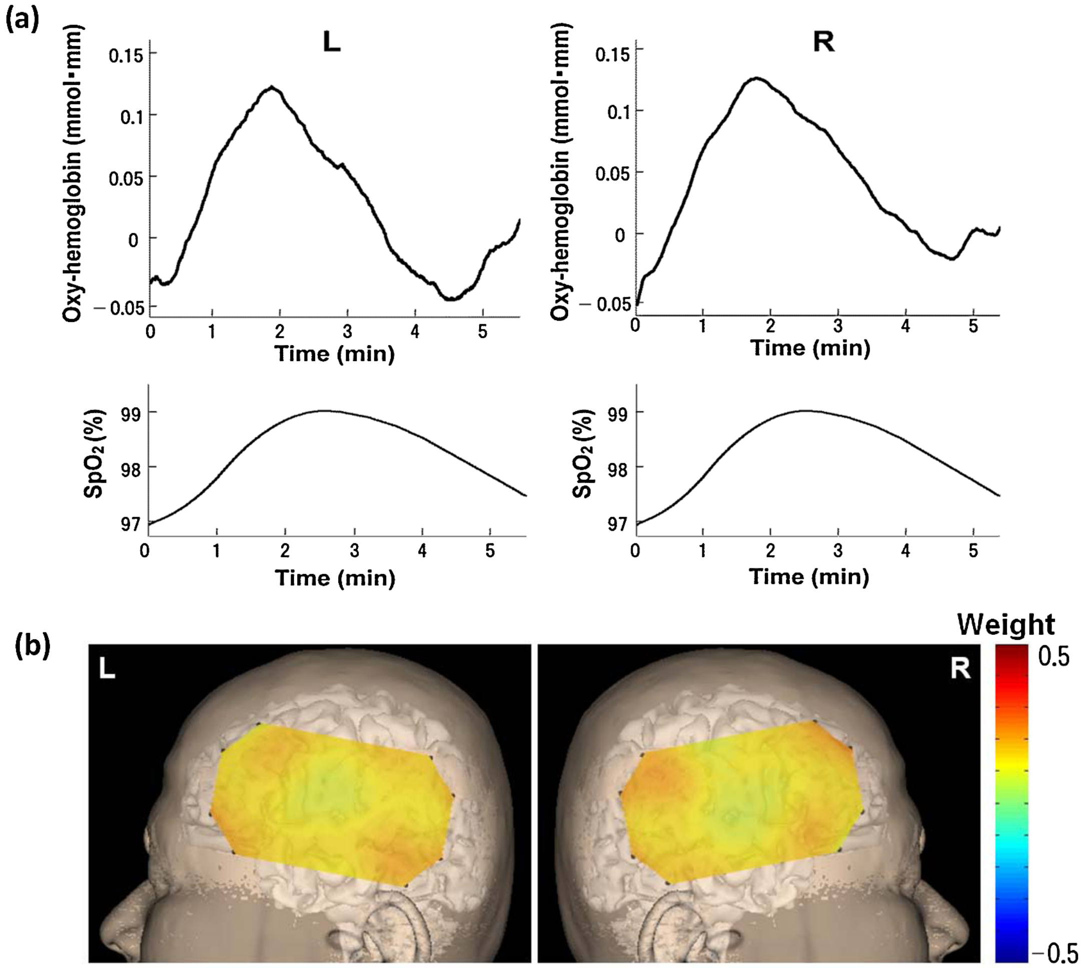

Fig. 3 Normal volunteer. (a) Changes in the concentration of oxygenated hemoglobin and SpO_2. (b) Topogram drawn using the weights of the first component, which had the highest correlation coefficient.

Table 1 Clinical features of cases with cerebral ischemia.

				Ischemic side	
Case	Atge	Sex	Vascular lesion	SPECT	OT
1–1	73	M	L ICA stenosis	L	L
1–2	73	M	L ICA stenosis (post-CAS)	N	N
2	68	M	L MCA occlusion	L	L
3	65	M	L ICA stenosis	L	L
4–1	78	M	R ICA stenosis	R	R
4–2	78	M	R ICA stenosis (post-CAS)	N	N
5	70	M	L ICA stenosis	L	L
6	78	M	L ICA stenosis	L	L
7	67	M	L ICA stenosis	L	L
8–1	66	M	R ICA stenosis	R	R

Table 1 (*Continued*).

				Ischemic side	
Case	Atge	Sex	Vascular lesion	SPECT	OT
8–2	66	M	R ICA stenosis (post-CAS)	N	N
9	58	M	R ICA stenosis	R	L
10	69	F	L MCA stenosis	L	L
11	69	F	R MCA occlusion	R	R
12	70	M	R ICA stenosis	R	R
13	61	M	R ICA occlusion	R	L
14	68	F	R MCA stenosis	R	L
15	78	M	R ICA occlusion	R	R
16	69	M	R ICA stenosis	R	L
17	78	M	L ICA stenosis	L	L
18	77	M	L ICA stenosis	L	L
19	61	M	L ICA stenosis	L	L
20	78	M	L ICA stenosis	L	L
21	67	M	L ICA stenosis	L	L
22	75	M	R ICA stenosis	R	R
23	67	M	L ICA stenosis	L	L
24	58	M	R ICA stenosis	R	R
25	60	M	R ICA occlusion	R	R
26	71	M	L ICA stenosis	L	L
27	61	M	R ICA occlusion	R	R
28	76	M	R ICA stenosis	R	R
29	60	M	L MCA stenosis	L	L
30	62	M	L ICA stenosis	L	L
31	65	F	L ICA stenosis	L	R
32	71	M	R ICA stenosis	R	R
33	78	M	R ICA stenosis	R	R

R: right, L: left, N: no laterality
MCA: middle cerebral artery; ICA: internal carotid artery
SPECT: single-photon-emission computed tomography
OT: optical topography
The columns named SPECT and OT indicate the side with cerebral ischemia in each modality.

3.2 *OT Data Analysis*

The time course data of HbOxy were analyzed using the following methods (Fig. 2). OT data were processed using MATLAB R2011b (MathWorks, Inc., Natick, MA).

Principal component analysis (PCA) was applied to the data and they were decomposed to principal components [Fig. 2(a)]. PCA has been widely used in data analysis to reduce data dimensionality without discarding essential features of the measurement data. PCA is a multivariate technique that utilizes synthetic variables (principal components), and it has been used to identify and remove signal interference from extracerebral tissues.[21–23] PCA was performed by creating a variance-covariance matrix of all measurement data and calculating its eigenvalue and eigenvector. Weights were the coefficients for each channel for synthesis of the principal component, and they reflect the degree of contribution of the data in each channel to the principal component data. Therefore, if the wave's height was low and/or the peak time was delayed, the weight is low.

Cross-correlation of each principal component and SpO_2 was calculated. It was determined that the principal component with the highest correlation coefficient included the information of changes in HbOxy associated with oxygen inhalation, and this was analyzed in detail.

In order to evaluate the transmission of the systemic SpO_2 changes to the cerebral tissues, weights of the principal components were calculated in each channel. The contour map (topogram) was drawn using the weights positioned at each measuring point. In the topogram, the values between each channel were calculated by spline interpolation [Fig. 2(b)].

3.3 *Evaluation of Cerebral Ischemia*

The laterality of OT was determined comparing the channel inspections in the symmetrical position on the topogram. The side with a lower weight was defined as the ischemic side. Statistical significance was determined using the Mann-Whitney U test as a nonparametric technique. Because not all the PCA weights had normal distributions, blood flows on the ischemic side and the contralateral side were considered unpaired groups. Differences with $P < 0.05$ were considered significant.

OT findings were compared to those of ^{123}I-IMP SPECT, and the possibility of identification of cerebral ischemia was investigated. Moreover, in patients who underwent carotid artery stenting (CAS), the findings of ^{123}I-IMP SPECT and OT were compared before and after CAS. Detection of improvement of CBF associated with CAS was also evaluated.

4 Results

In normal volunteers, changes in SpO_2 exhibited a trapezoidal pattern associated with oxygen inhalation, and the changes in HbOxy measured using OT showed a similar time course [Fig. 3(a)]. In the case shown in Fig. 3, there was no significant laterality of the weights of PCA ($P = 0.72$, Mann-Whitney U-test), and this finding was identified in the topogram [Fig. 3(b)]. These findings were observed in 25 (83%) of the normal volunteers.

On the other hand, with cerebral ischemia, the increase in HbOxy was delayed and/or lowered, and the PCA weights in the ischemic side were lower compared to the normal side. Therefore, the side with cerebral ischemia could be detected. Results in cases of cerebral ischemia are shown in Table 1. The ischemic side defined by ^{123}I-IMP SPECT and OT are shown in Table 1 as well. In 28 (85%) of the cerebral ischemia cases, the findings of OT agreed with those of ^{123}I-IMP SPECT. Moreover, in three patients who underwent CAS, OT findings were compared to those of ^{123}I-IMP SPECT and changes in CBF associated with CAS were compared. In the findings of ^{123}I-IMP SPECT for post-CAS patients, improvement in CBF was observed. On the other hand, in the findings of OT after CAS, increases in the PCA weights in the ischemic regions were observed. Laterality of the PCA weights was not observed after CAS. Over the time period of the measurement, HbTotal decreased slightly and HbR exhibited a wave pattern almost reverse to HbOxy.

4.1 *Typical Case of Cerebral Ischemia*

A 73-year-old male patient had severe stenosis of his left cervical ICA that was observed angiographically [Fig. 4(a)].

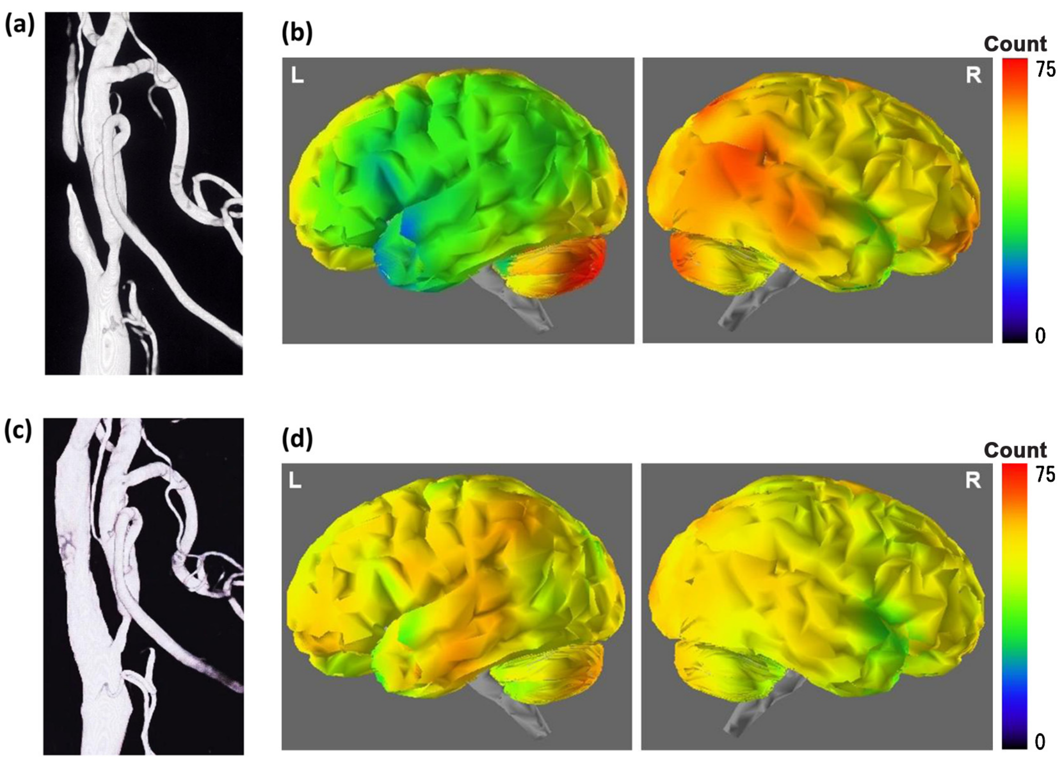

Fig. 4 Case of cerebral ischemia (angiogram and IMP-SPECT). (a) Angiogram shows a severe stenosis of the left cervical ICA. (b) IMP-SPECT demonstrates a decrease in CBF in the area of the left MCA. (c) Angiogram shows dilation of the ICA after CAS. (d) IMP-SPECT demonstrates an increase in CBF in the area of the left MCA after CAS.

^{123}I-IMP SPECT demonstrated a decrease in CBF in the left cerebral hemisphere [Fig. 4(b)]. CAS was performed on the left cervical ICA [Fig. 4(c)]. Improvement of CBF was observed in ^{123}I-IMP SPECT after CAS [Fig. 4(d)]. On the other hand, in the left cerebral hemisphere, the increase in HbOxy measured using OT with oxygen inhalation was lower than that of the contralateral side before CAS [Fig. 5(a), Table 1: Case 1-1]. However, the laterality of the changes in HbOxy disappeared after CAS because the changes in HbOxy were associated with CAS [Fig. 5(c), Table 1: Case 1-2].

In this case, OT measurement data were analyzed statistically by PCA, and the correlation coefficients of each principal component and SpO_2 were calculated. Before CAS, the correlation coefficient of the first principal component and SpO_2 was the highest ($r = 0.79$), so the first principal component was selected as the component that included information associated with oxygen inhalation. Weights from both sides were compared in this principal component, and the weights in the left side were significantly decreased compared to the weights in the contralateral side ($P = 0.00058$, Mann-Whitney U-test). Topogram findings agreed with the regions of cerebral ischemia detected in ^{123}I-IMP SPECT [Fig. 5(b)].

After CAS, the correlation coefficient of the first principal component and SpO_2 was found to be the highest ($r = 0.93$), and this principal component was selected as the component that included information associated with oxygen inhalation. Weights of this principal component were calculated, and the weights from both sides were compared. There was no significant laterality of the PCA weights ($P = 0.82$, Mann-Whitney U-test). Topogram findings agreed with the regions with improvement of CBF in ^{123}I-IMP SPECT after CAS [Fig. 5(d)]. Averages of the PCA weights in normal volunteers and ischemic patients are shown in Fig. 6.

5 Discussion

In normal volunteers, the changes in HbOxy exhibited a trapezoidal pattern according to oxygen inhalation, and there was no laterality of the PCA weights based on the SpO_2 wave pattern in 83% of cases. Therefore, this finding was regarded as typical of OT in normal tissues. The laterality of findings was also investigated. In all cases with no laterality of the PCA weights, HbTotal was slightly decreased and did not fluctuate. However, in cases with laterality, HbTotal was unstable. This instability was thought to be because cerebral hemodynamic fluctuation of a systemic origin was insufficiently removed from the cases with laterality.

On the other hand, in the ischemic cases, increases in HbOxy were lower in the ischemic regions compared to the normal regions. The PCA weights based on the SpO_2 wave pattern

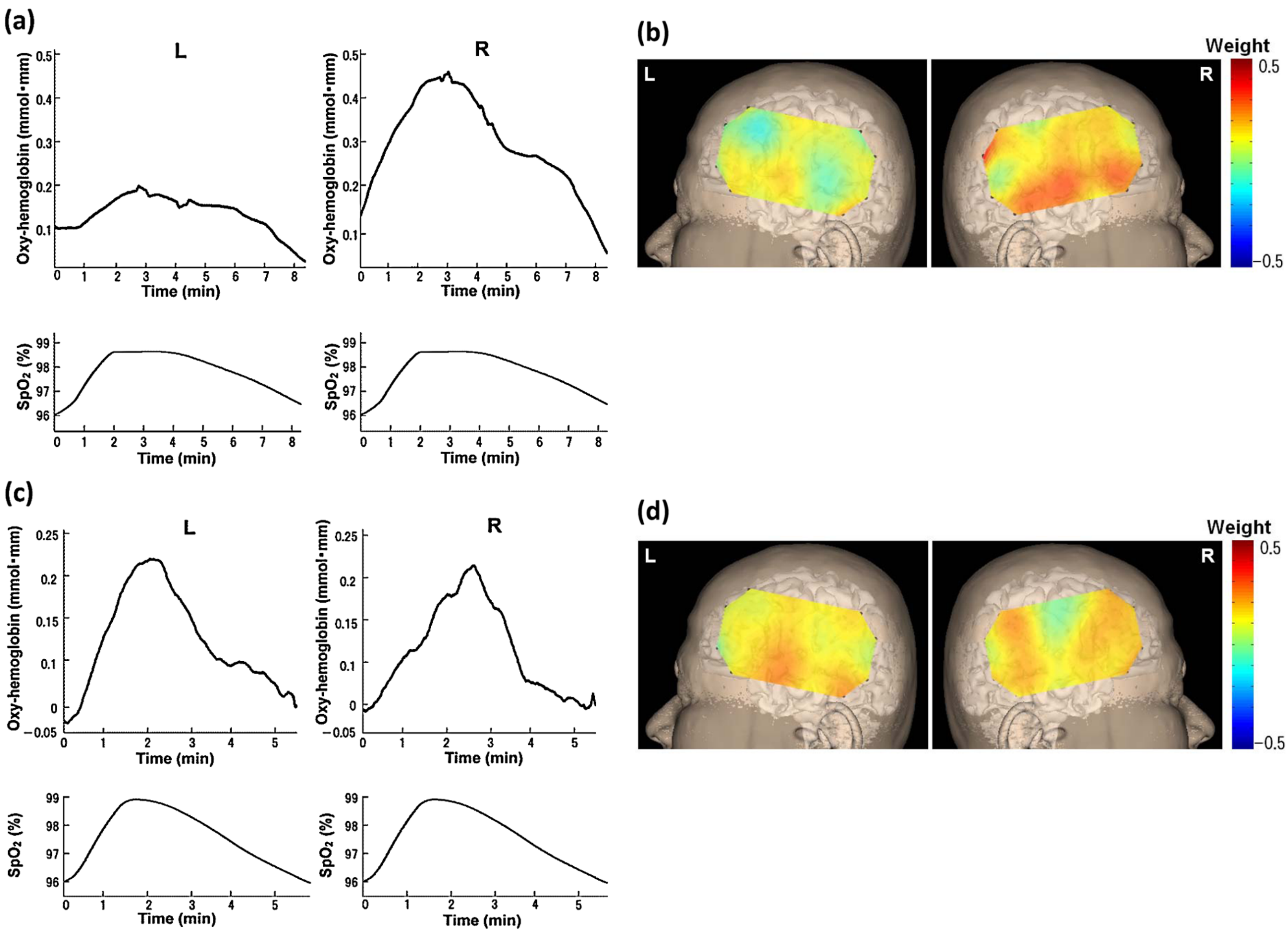

Fig. 5 Case of cerebral ischemia (NIRS). (a) Changes in the concentration of oxygenated hemoglobin and SpO_2 before CAS. (b) Topogram drawn using the weights of the first component, which had the highest correlation coefficient before CAS. (c) Changes in the concentration of oxygenated hemoglobin and SpO_2 after CAS. (d) Topogram drawn using the weights of the first component, which had the highest correlation coefficient after CAS.

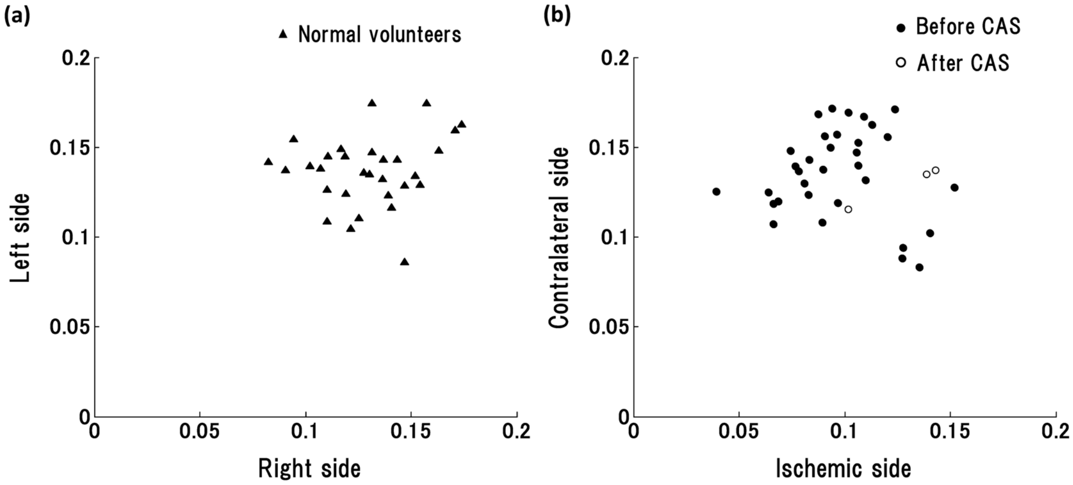

Fig. 6 Scatter plot of the average PCA weights. (a) The *x*-axis showing the average PCA weights on the right side, and *y*-axis showing the average PCA weights on the left side in normal volunteers. (b) The *x*-axis showing the average PCA weights on the ischemic side as defined by IMP-SPECT, and the *y*-axis showing the average PCA weights on the contralateral side in ischemic patients.

were lower in the ischemic regions in the topogram. These findings agreed with those of ^{123}I-IMP SPECT in 85% of ischemic cases. The reason for this was considered to be that transportation and diffusion of oxygen were attenuated in the ischemic regions by stenosis or occlusion of the ICA or MCA. In ischemic cases with no laterality in the PCA weights, CBF decreased slightly compared to the contralateral side in the findings of ^{123}I-IMP SPECT. It was thought that detection of mild ischemia was difficult with the present method. Cerebral oxygenation in regions with mild ischemia was the same as in normal regions. This is because the decrease in CBF leads to an increase in oxygen extraction fraction in order to preserve oxygen metabolism.[24,25]

Moreover, in the ischemic cases, findings of ^{123}I-IMP SPECT before and after CAS were compared. In the regions where CBF was lower than the normal regions before CAS, increases in CBF were observed after CAS and laterality was not observed. In these cases, changes in HbOxy measured using OT increased after CAS in regions where they had been lower than the normal regions before CAS. PCA weights increased after CAS, and this result was also observed in the topogram that was drawn using the weights. Regions where the weights increased agreed with regions that showed improvement in CBF as detected by ^{123}I-IMP SPECT.

It is important to note that there is unavoidable influence that comes from the CBV of the scalp because the concentration of hemoglobin is measured through the scalp. It has been reported that oxygen inhalation raises skin blood flow moderately, but that the change in flow is not significant.[17] Although PCA could not entirely remove the extracerebral contribution from OT signals collected with several channels, it was useful for reducing signal interference from extracerebral tissues.

In the present cases of cerebral ischemia, improvement of blood flow associated with CAS was only in the ICA, and blood flow in the external carotid artery (ECA) did not change. Therefore, differences in the findings of OT before and after CAS must be attributed mainly to changes in CBF from the ICA, with only a small influence due to blood flow from the ECA.

OT has mainly been used to visualize brain functions in which changes in CBV are measured during a physiological task. On the other hand, in the present method, HbOxy in cerebral tissues is measured during oxygen inhalation. It has been reported that cerebral perfusion can be measured by OT using an intravenous bolus of indocyanine green.[26,27] The present method is similar to that technique and can be used to detect a difference in the efficiency of transport and diffusion of oxygen to the cerebral tissues.

6 Conclusion

An OT method with oxygen inhalation was developed for the evaluation of cerebral ischemia, and this method could be used to identify the ischemic side. The present method was clinically useful because the cerebral ischemia could be measured easily, repeatedly, and noninvasively.

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