Brain oxymetry in the operating room: current status and future directions with particular regard to cytochrome oxidase

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Abstract. Near-infrared spectroscopy (NIRS) is a cerebral monitoring method that noninvasively and continuously measures cerebral hemoglobin oxygenation and the redox state of cytochrome oxidase using highly tissue-permeable near-infrared light. This technique now has wide clinical application, and its usefulness in the measurement of cerebral hemoglobin oxygenation has been confirmed under global cerebral injury and/or hypoxemic hypoxia; however, regional cerebral infarction located far from the monitoring site may not be detected by NIRS. Furthermore, the specificity and accuracy of the measurement of the redox state of cytochrome oxidase remain controversial. We apply NIRS to both animal and clinical investigations. Based on these results, we discuss the significance of the measurement of cerebral hemoglobin oxygenation and cytochrome oxidase *in vivo* and in clinical medicine. Using our algorithm, cytochrome oxidase signals are unaffected by hemoglobin signals, even when hematocrit values change from 35 to 5% under cardiopulmonary bypass in a dog model. In the clinical study, cytochrome oxidase during surgery is likely to be a good (though not perfect) predictor of postoperative cerebral outcome. NIRS appears to be a promising technology, but additional investigations are required to establish its clinical efficacy and justify its routine use during operative and perioperative periods. [DOI: 10.1117/1.2940583]

Keywords: near-infrared spectroscopy; cytochrome oxidase; cerebral monitoring.

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1 Introduction

Central nervous system and psychiatric disorders are more likely to occur following cardiovascular surgery when compared to other surgeries.[1] A large prospective study that evaluated 2108 patients undergoing coronary artery bypass graft (CABG) surgery at 24 institutions recorded adverse cerebral outcomes in 6.1% of patients overall,[2] 3.1% of these patients experienced focal injury, stupor, or coma, with an associated in-hospital mortality rate of 21%. Although the incidence of stroke appears to be less than 1% for patients under the age of 65 years, the cumulative stroke risk for patients over age 65 is 5%; in two separate studies, the stroke rate in patients over age 75 years was 7 to 9%.[3,4] Because cerebral injury continues to be a major source of morbidity and mortality after cardiovascular surgery, protection of the brain is a primary concern during operative and perioperative periods.[5–7] Incriminated as a major factor in this complication is the presence of a level of cerebral perfusion that is inadequate to meet the cerebral metabolic demands during cardiopulmonary bypass (CPB) and/or selective cerebral perfusion, even though the patient is under deep hypothermia. Consequently, it is not the level of cerebral blood flow per se during cardiovascular surgery that is likely to be important, but an appropriate balance between cerebral perfusion and cerebral oxygen consumption.

Near-infrared spectroscopy (NIRS) is now in widespread use in such clinical fields as anesthesiology,[8] neurosurgery,[9] and pediatrics.[10,11] NIRS is a noninvasive technique that enables physicians to continuously monitor variation in the oxygenation of hemoglobin and the redox state of cytochrome oxidase in living tissue. The cytochrome oxidase signal from NIRS has a controversial history. A seminal work in the study of cytochrome oxidas by NIRS is that of Matcher et al.,[12] which showed that algorithms from different groups produced markedly different results when analyzing the same dataset, thereby highlighting the unreliable nature of the cytochrome oxidase signal. In the present work, we review NIRS by discussing the usefulness and limitations of the technique with particular regard to cytochrome oxidase, using an animal model and actual clinical data.

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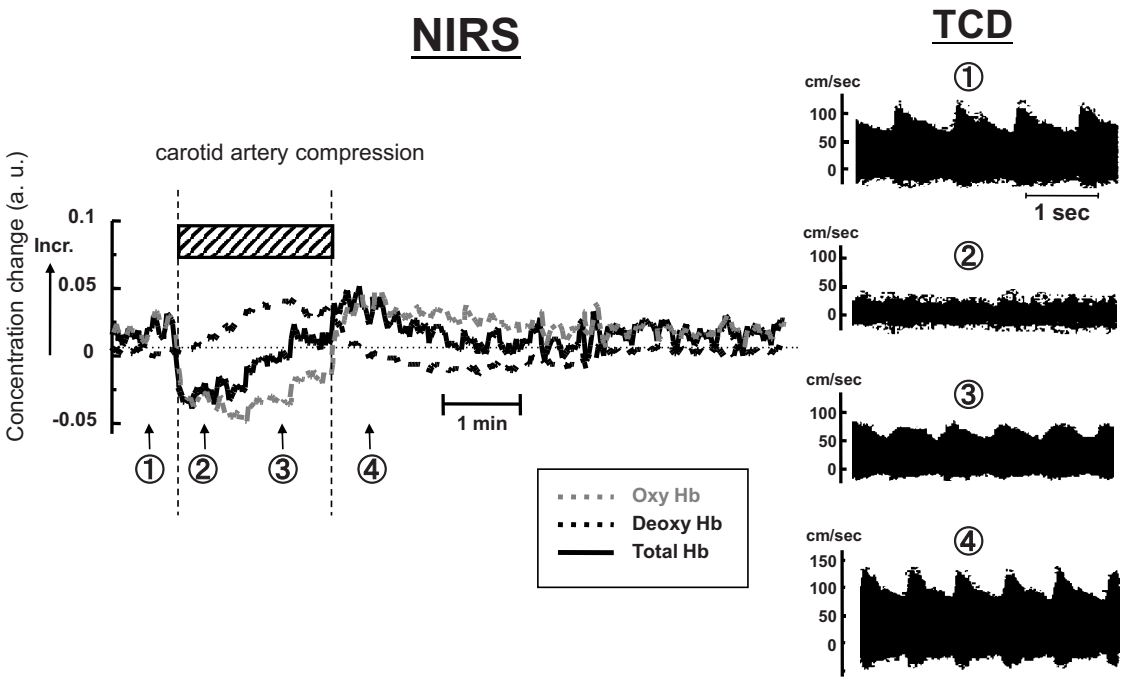

Fig. 1 Changes in cerebral oxygenation and middle cerebral artery blood flow during carotid artery compression. Probes for near-infrared spectroscopy (NIRS) and transcranial Doppler ultrasonography (TCD) were attached on the same side (NIRS numbers correspond to TCD numbers).

2 Reality of Intracerebral Hemoglobin Measurement by Near-Infrared Spectroscopy in the Clinical Setting

As expected, the risk of stroke after cardiac surgery increases with the severity of carotid disease: a follow-up study of 4047 patients examined before CABG reported that the risk of stroke increased from 1.9 to 6.3% in the presence of >50% carotid stenosis.[13] It is therefore important to survey the existence and severity of carotid disease. The carotid compression study was done against healthy volunteers (n=4) and patients with cerebral vascular disease (n=7). Figure 1 shows the typical changes in cerebral oxygenation and blood flow of the middle cerebral artery in a healthy volunteer, as assessed by NIRS and transcranial Doppler (TCD), respectively. Following compression of one carotid artery at the monitoring site, oxygenated hemoglobin ([oxy-Hb]) decreased and deoxygenated hemoglobin ([deoxy-Hb]) increased (as shown by point 2 in Fig. 1). At this time, blood flow in the middle cerebral artery decreased and arterial pulsation was absent; however, it is interesting that at several seconds after the start of compression, [oxy-Hb] and [deoxy-Hb] began to increase and decrease, respectively, and blood flow in the middle cerebral artery resumed (as shown by point 3 in Fig. 1). When the carotid artery was compressed at the monitoring site in some other healthy volunteers, similar reactions (delayed improvement of cerebral oxygenation and blood flow) were seen with some individual differences. The reason for this finding is the circle of Willis, a vascular structure at the base of the brain. This arterial ring directly connects the left and right carotid arteries via the anterior cerebral and anterior communicating arteries, and serves as important collateral circulation when one carotid artery is occluded. What happens if this collateral circulation is blocked? In 5 of 7 patients with cerebral vascular disease, cerebral oxygenation decreased and the blood flow rate in the middle cerebral artery was reduced when one carotid artery was compressed; the ischemic and hypoxic condition of the brain did not improve during the compression period. Figure 2 shows changes in cerebral oxygenation and the blood flow rate of the middle cerebral artery in a patient who was preoperatively diagnosed with occlusion of the anterior communicating artery. When one carotid artery was compressed, cerebral oxygenation decreased, with a reduction in blood flow rate in the middle cerebral artery; the ischemic and hypoxic condition of the brain did not improve during compression period (as shown by point 2 in Fig. 2). TCD has the advantage of being quantitative and that it actually measures the restoration of flow rather than a surrogate of flow; however, TCD is often hampered by impenetrable ultrasound windows.[14] Thus, a brief compression test of the carotid artery using both NIRS and TCD monitoring could enable a survey of cerebrovascular disease, especially in regard to the severity of carotid disease and dysfunction of the circle of Willis.

3 Cytochrome Oxidase Measurement Problems by Near-Infrared Spectroscopy and Introduction of Our Algorithm

The monitoring of brain oxygen status using NIRS was first applied to clinical practice by Jöbsis in 1977.[15] Published studies indicat that NIRS could be used as a continuous and noninvasive method of observing changes in the cerebral oxygenation state during hypoxia and ischemia, because changes occur in the optical properties under these conditions; however, the interpretation of NIRS data, especially the cytochrome oxidase signal, remains controversial.[16–18] Mitochondrial cytochrome oxidase consists of two hemoproteins (heme

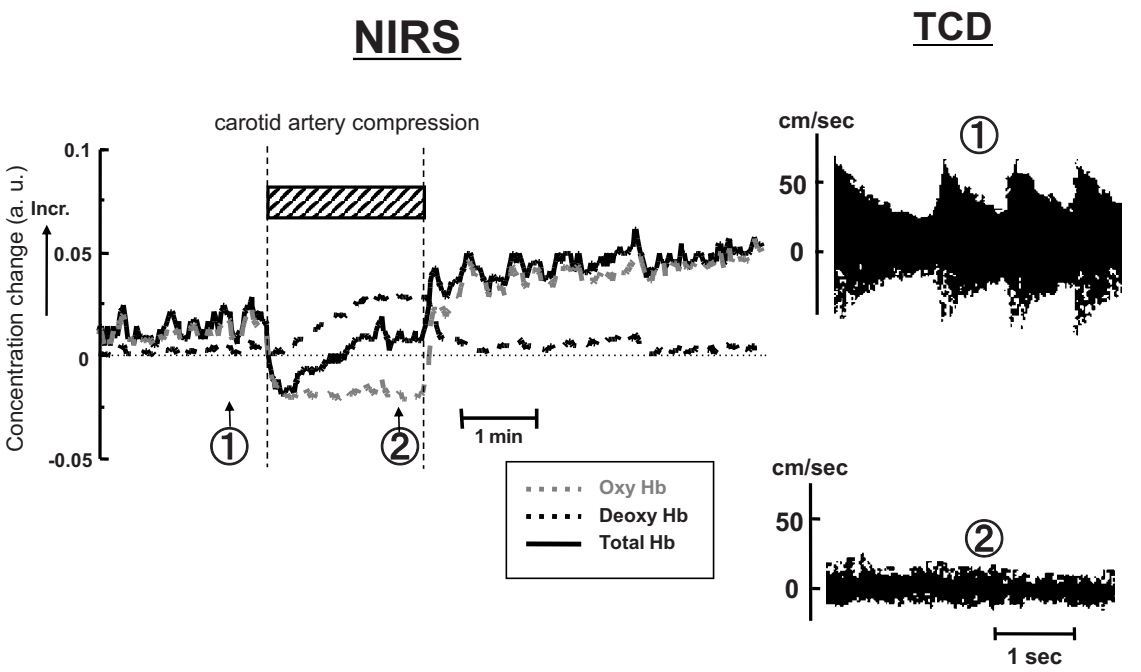

Fig. 2 Changes in cerebral oxygenation and middle cerebral artery blood flow during carotid artery compression in a patient with anterior communicating artery occlusion. Probes for near-infrared spectroscopy (NIRS) and transcranial Doppler ultrasonography (TCD) were attached on the same side (NIRS numbers correspond to TCD numbers).

a and heme a3) and two copper proteins (CuA and CuB). A wide absorption spectrum is seen in the infrared region, with a peak at 830 nm for CuA; detection by NIRS of changes in its absorption enables the noninvasive and real-time assessment of the redox state of cytochrome oxidase. A possible source of error that might interfere with accurate measurements of the redox state of cytochrome oxidase is the derives overlapping of the absorption spectra for hemoglobin and cytochrome oxidase in the near-infrared region, with the absorption coefficient for hemoglobin being an order of magnitude greater than that for cytochrome oxidase.[19] Several studies have shown that while the absorption coefficient of cytochrome oxidase was originally considered a constant, it appears to vary markedly in isolated mitochondria and in the blood-free perfused rat brain model, depending on the energy conditions.[20,21] In other words, cytochrome oxidase cannot be accurately measured using a formula in which a constant is used for the absorption coefficient of cytochrome oxidase.

Clinical data shown in the present work were calculated using a formula derived by researchers at Hokkaido University (Tamura group).[22] One important assumption of our algorithm is that in the near-infrared region (700 to 900 nm), the absorbance changes in the range shorter than 780 nm are mainly attribute to Hb, whereas those at wavelengths longer than 780 nm are attributed to both Hb and oxidized cytochrome oxidase. Thus, the changes in hemoglobin oxygenation and the redox state of cytochrome oxidase were calculated by the following algorithm:

$$\Delta[\text{oxy-Hb}] = -0.912\Delta A_{700-750} + 2.128\Delta A_{730-750},$$

$$\Delta[\text{deoxy-Hb}] = 0.744\Delta_{700-750} - 1.613\Delta A_{730-750},$$

$$a_3''\Delta[\text{cyt ox}] = 1.53\Delta A_{700-750} - 0.768\Delta A_{730-750} + \Delta A_{805-750},$$

where a_3'' is the proportionality factor (normalized absorption coefficient) for CuA. Because scattering effects prevent determination of the optical path length, the results are expressed in relative values of concentration changes with an arbitrary unit (a. u.) rather than absolute ones. This unique equation quantifies cytochrome oxidase based on an experimentally determined hemoglobin coefficient, without using a coefficient for cytochrome oxidase. It must be noted here that the coefficients of our equation contain instrumentation factors such as the half-width of the optical filters used, in addition to the optical path length. When a new instrument is assembled, we therefore have to re-estimate these factors. Matcher et al.[12] reported that they found differences when applying four published NIRS algorithms (by the London group, Duke group, Keele group, and our group) to the same *in-vivo* dataset. However, the results from our algorithm[23] in their report were different from those that we obtained by the use of our NIRS instrument. This discrepancy might have resulted because they did not take instrumentation factors into account when applying our algorithm. The other three groups employ a variety of different measurement wavelengths and algorithms to measure the changes in hemoglobin oxygenation and redox state of cytochrome oxidase.[12] In a recent study regarding NIRS measurement of cerebral cytochrome oxidase changes in patients with orthostatic hypotension, Tachtsidis et al.[24] reported a simple mechanism for cross talk, thought to produce artifactual changes in cytochrome oxidase, finding that it was not present between the hemoglobin and the cytochrome oxidase signal. Although Uludag et al.[25] consider that the existence of cytochrome oxidase changes in response to func-

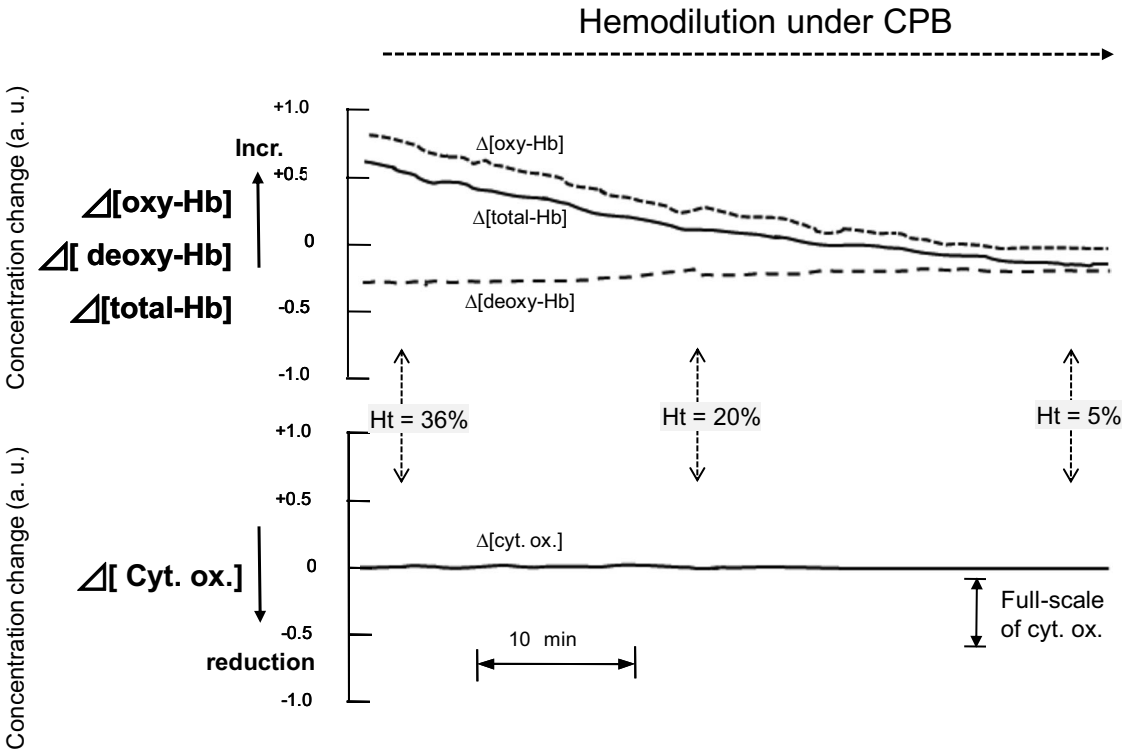

Fig. 3 Relative changes in cerebral hemoglobin oxygenation and the redox state of cytochrome oxidase in dog brain measured by NIRS during hemodilution under cardiopulmonary bypass (CPB). The relative concentrations of [oxy-Hb] and [total-Hb] decreased significantly during hemodilution, while cytochrome oxidase recorded no change. Full-scale value of the redox state of cytochrome oxidase was determined by aerobic (100% O_2)-to-anaerobic (100% N_2) transition using a membrane oxygenator.

tional stimulation measured by NIRS cannot be explained by a mere cross-talk artifact, they suggest that invasive studies in animals and intraoperative studies in humans should be used to evaluate the parameter's relevance in functional activation of the cerebral cortex. Sakamoto et al.[26] reported that NIRS was unable to separate hemoglobin and cytochrome oxidase components during hemodilution under CPB in a piglet model, leading to artifactual changes in the cytochrome signal.

We applied our algorithm to an animal model[27] almost identical to that described by Sakamoto et al.[26] After the institution of CPB, an aerobic (100% O_2)-to-anaerobic (100% N_2) transition was induced using a membrane oxygenator to determine the maximum changes in the full-scale value of the redox state of cytochrome oxidase. After stabilization under 100% O_2, the animal received 200 mg/kg of sodium cyanide intravenously to inhibit electron transport from cytochrome oxidase to the oxygen molecule. Hematocrit was then reduced under CPB from 35 to 5% by hemodilution using Ringer's solution. Figure 3 shows that after the infusion of sodium cyanide, [oxy-Hb] and [total-Hb] were significantly decreased during hemodilution, but that the cytochrome oxidase signal showed little change and that the variance of cytochrome oxidase during hemodilution was less than 4% of full scale (100% O_2-to-100% N_2 transition) under CPB in the dog model. The relative concentration of [total-Hb] (as measured by NIRS) showed a strong positive correlation with hematocrit values in the blood, but there was no correlation between the cytochrome oxidase signal and hematocrit values during hemodilution (Fig. 4).[27] Using our algorithm, cytochrome oxidase signals are completely unaffected, even when hematocrit values change from 35 to 5%. This may resolve the problems associated with cytochrome oxidase measurement that arise by blood dilution associated with cardiovascular surgery.

4 Cytochrome Oxidase Measurement Using Near-Infrared Spectroscopy in Clinical Medicine

Because cytochrome oxidase is the terminal enzyme in the respiratory chain in mitochondria, its redox state is directly related to the intracellular oxygenation state and to the energy state of the tissue. Cooper et al.[28] showed that when blood is withdrawn stepwise in rats, [oxy-Hb] falls linearly with decreases in the rate of oxygen delivery to the brain, whereas the redox state of cytochrome oxidase is unchanged until the oxygen delivery rate is reduced to below approximately one-half of the normal physiological level. However, other studies showed that cytochrome oxidase can be oxidized by increasing oxygen availability to the brain tissue under conditions of hyperoxia or hypercapnia, and have argued that cytochrome oxidase might be partially reduced.[29–31] The question of whether cytochrome oxidase is partially reduced in normoxia remains unanswered.

In our previous study, under conditions of hyperoxia and/or hypercapnia *in-vivo* rat models, cytochrome oxidase did not cause further oxidation, whereas [oxy-Hb] was increased.[22] When the electron flow rate through the respira-

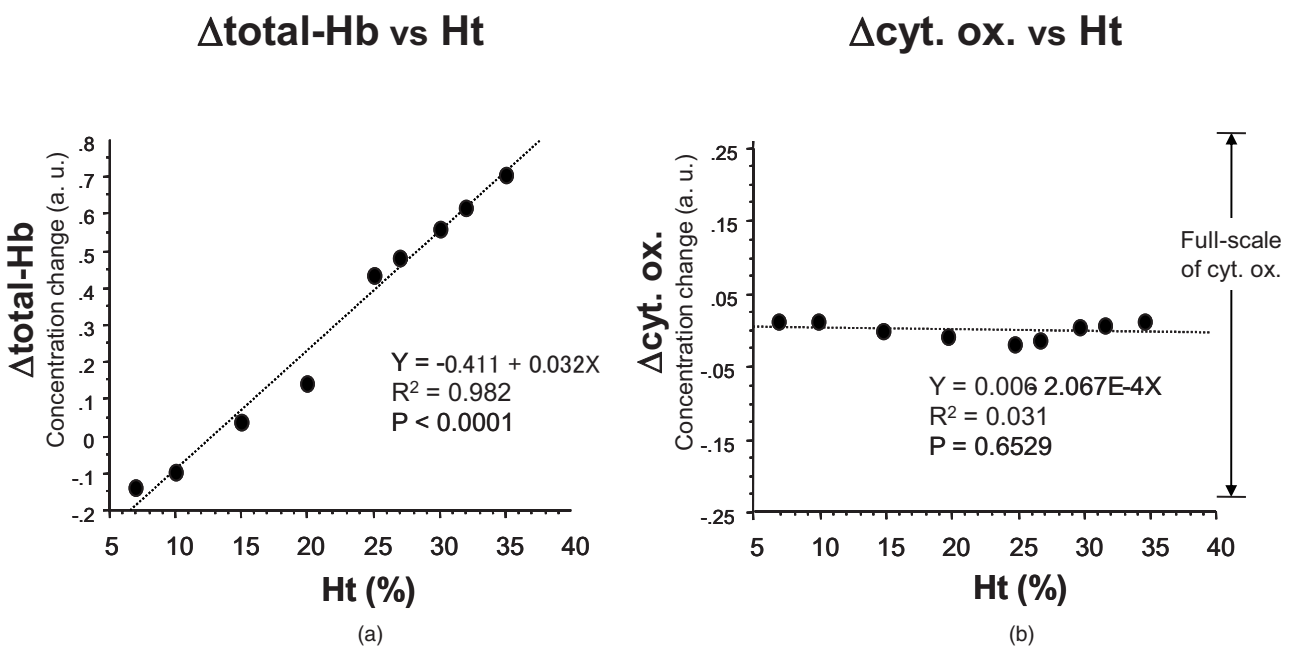

Fig. 4 Relationship between blood hematocrit (Ht) values and relative changes in concentrations of (a) [total-Hb] and (b) cytochrome oxidase in dog brain (as measured by NIRS) during hemodilution. The relative concentration of [total-Hb] showed a strong positive correlation with blood Ht values. However, there was no correlation between the cytochrome oxidase signal and Ht values. Full-scale value of the redox state of cytochrome oxidase was determined by aerobic (100% O_2)-to-anaerobic (100% N_2) transition using a membrane oxygenator.

tory chain is decreased by blocking of the glucose metabolism in the blood-free perfused rat brain model, the redox state of CuA was slightly hyperoxidized, although not significantly so.[21] Different values of a half-maximal reduction (P50) of the cytochrome oxidase for coupled mitochondria have been quoted by different authors: Sugano et al.[32] quoted 0.03 to 0.27 μM, depending on the metabolic activity; Gnaiger[33] quoted 0.24 uM; and Wilson et al.[34] quoted approximately 0.7 μM. Hoshi, Hazeki, and Tamura[20] demonstrated that the oxygen dependence of the redox state of heme a+a3 depends on the mitochondrial energy state as well as the respiratory rate, but that CuA is independent of these factors (the P50 of heme a+a3 was 0.078 and 0.16 μM in states 4 and 3, respectively; the P50 of CuA was 0.075 μM). These calibration studies showed that the P50 of cytochrome oxidase is much higher than that of Hb (P50 of Hb is 42 μM), by approximately three orders of magnitude. Based on the results obtained from both animal[21,22] and clinical investigations,[35] cerebral cytochrome oxidase, especially CuA, may be fully oxidized under normal physiological conditions. Thus, the start of reduction can be used as an alarm, indicating that the brain has reached critical metabolic and functional levels.

Figure 5 shows changes in intracerebral oxygenation in a patient scheduled to undergo aortic arch replacement due to dissecting aortic aneurysm.[35] When extracorporeal circulation was initiated by supplying blood from the femoral artery, intracerebral cytochrome oxidase reduction was detected. As brain cells were thought to be in a critical state, arterial cannulae were quickly inserted into both right and left common carotid arteries and separate cerebral perfusion (SCP) was initiated; the redox state of cytochrome oxidase then rapidly returned to preoperative levels, and pupil dilation disappeared. Intraoperative findings revealed a flap at the base of the right brachiocephalic artery, and when blood was supplied from the femoral artery, the right common carotid artery became completely occluded.[35] As we know from numerous clinical experiments, hypothermia is beneficial in achieving cerebral protection during cerebral hypoxia and/or hypoperfusion; indeed, increases in PCr and ATP in the brain are observed during cooling.[36,37] When our algorithm was used in the present study to measure the redox state of cytochrome oxidase, under deep hypothermia (nasopharyngeal temperature: 15°C), the redox state showed oxidation after the initiation of SCP rather than the preoperative level (Fig. 5)[35]; however, some groups reported that while the relative cerebral hemoglobin saturation increased during hypothermia, cytochrome oxidase showed a marked reduction.[17,38,39] The previous studies suggested several potential explanations for this phenomenon, such as the increased affinity of hemoglobin for oxygen and the decreased efficiency of cytochrome oxidase in transferring electrons to oxygen, among others.[38] In this respect, the redox behavior of cytochrome oxidase in the present study appears to reveal oxidation rather than reduction under deep hypothermia, which was inconsistent with the conclusions of their previous study.[17,38,39] Thus, further investigations are required to re-evaluate the redox behavior of cytochrome oxidase under hypothermia.

5 Reality of Cytochrome Oxidase Measurement by Near-Infrared Spectroscopy in the Clinical Setting

Cerebral injury continues to be a major source of morbidity and mortality after thoracic aortic surgery; therefore, protection of the brain is a primary concern during the operative and perioperative periods.[5–7] The presence of a level of cerebral

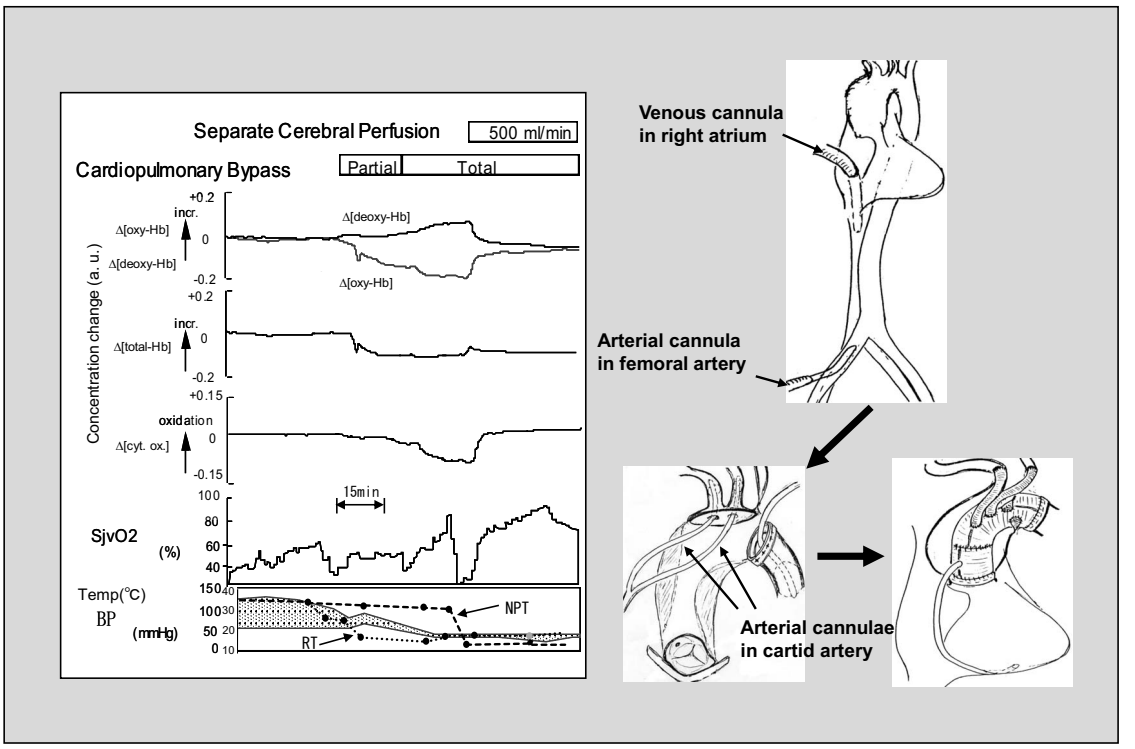

Fig. 5 Changes in intracerebral oxygenation during extracorporeal circulation with separate cerebral perfusion in a patient with dissecting aortic aneurysm. $SjvO_2$ is the jugular venous oxygen saturation; BP is blood pressure; temp is temperature; NPT is the nasopharyngeal temperature; and RT is rectal temperature.

perfusion that is inadequate to meet the cerebral metabolic demands during CPB and/or selective cerebral perfusion, even though the patient is under deep hypothermia, has been incriminated as a major factor in this complication. To evaluate whether cerebral Hb oxygenation and the redox state of cytochrome oxidase during surgery, as measured by NIRS, are accurate predictors of postoperative cerebral outcome, we retrospectively examined the relationship between these two parameters in 66 patients who underwent thoracic aortic surgery.[40]

In all cases, the various changes occurred in cerebral Hb oxygenation ([oxy-Hb], [deoxy-Hb], and [total-Hb]) at the initiation of CPB, and during the periods of hypothermia and rewarming. We classified the changes in the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) in the 66 cases at the completion of surgery as either a marked and prolonged increase (type X), a subsequent return to baseline (type Y), or a marked and prolonged reduction (type Z). When we retrospectively assessed the redox behavior of cytochrome oxidase during the operation in detail, we realized that there were three different types of cytochrome oxidase behavior. In terms of time course, we classed these as either no change (type A), a temporary, marked reduction with a subsequent return to baseline (type B), or a marked and prolonged reduction (type C) (Fig. 6). Figures 7–9 show the typical type of cytochrome oxidase behavior. The characteristics of the type-A pattern are that the redox state of cytochrome oxidase remains at its initial level (no change) throughout the operation, even though marked changes occur in [oxy-Hb], [deoxy-Hb], and [total-Hb] at the initiation of CPB and/or during the periods of hypothermia and rewarming; 34 of the 66 cases (51.5%) were of this type (Fig. 7). In the type-B pattern, a transient reduction of cytochrome oxidase is observed, but recovery to baseline occurs by the end of the operation; 29 of the 66 cases (43.9%) showed this pattern (Fig. 8). Figure 9 shows the changes in cerebral oxygenation in a case representative of type C; only 3 of the 66 cases (4.5%) were of this type. The characteristics of type C are that the redox behavior of cytochrome oxidase shows a marked and prolonged reduction both during and following the operation.[40]

In the present study, 9 of the 66 patients (13.6%) suffered from postoperative brain injury (Table 1). This resulted in severe coma (four cases), hemiparesis (three cases), convulsion (one case), and sight deficit (one case). We tested for significant differences between the occurrence of brain injury and the pattern of changes in the signals of hemoglobin and cytochrome oxidase using the chi-square test for independence ($l \times m$ contingency table). There was no significant relationship between the occurrence of brain injury and the cerebral oxygen index type ([oxy-Hb] minus [deoxy-Hb]). In contrast, the relationship between the occurrence of brain injury and the cytochrome oxidase behavior type was highly significant (Table 2).[40]

Although it appears that the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) by NIRS can measure regional changes in cerebral oxygen metabolism caused by blood dilution, cooling, rewarming, and changes in FIO_2, there was no significant relationship in the present study between the occurrence of severe brain injury and the magnitude of the ce-

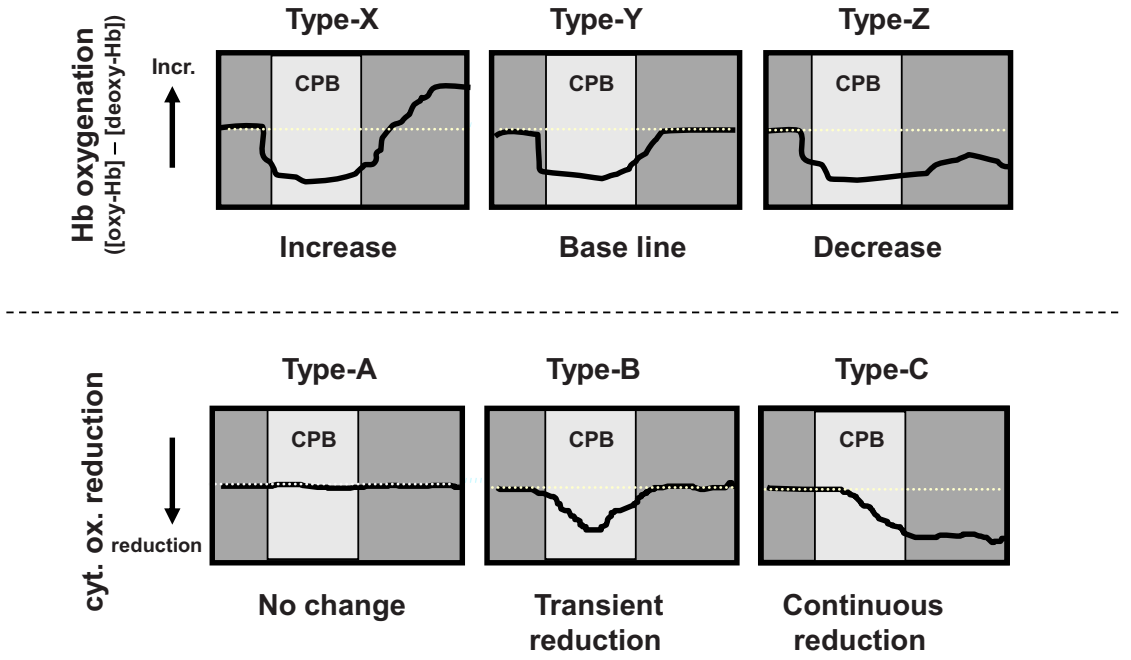

Fig. 6 Diagrammatic representation of the three different patterns of change in the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]), and in cytochrome oxidase observed during surgery. Each panel represents the period from before surgery to the end of anesthesia.

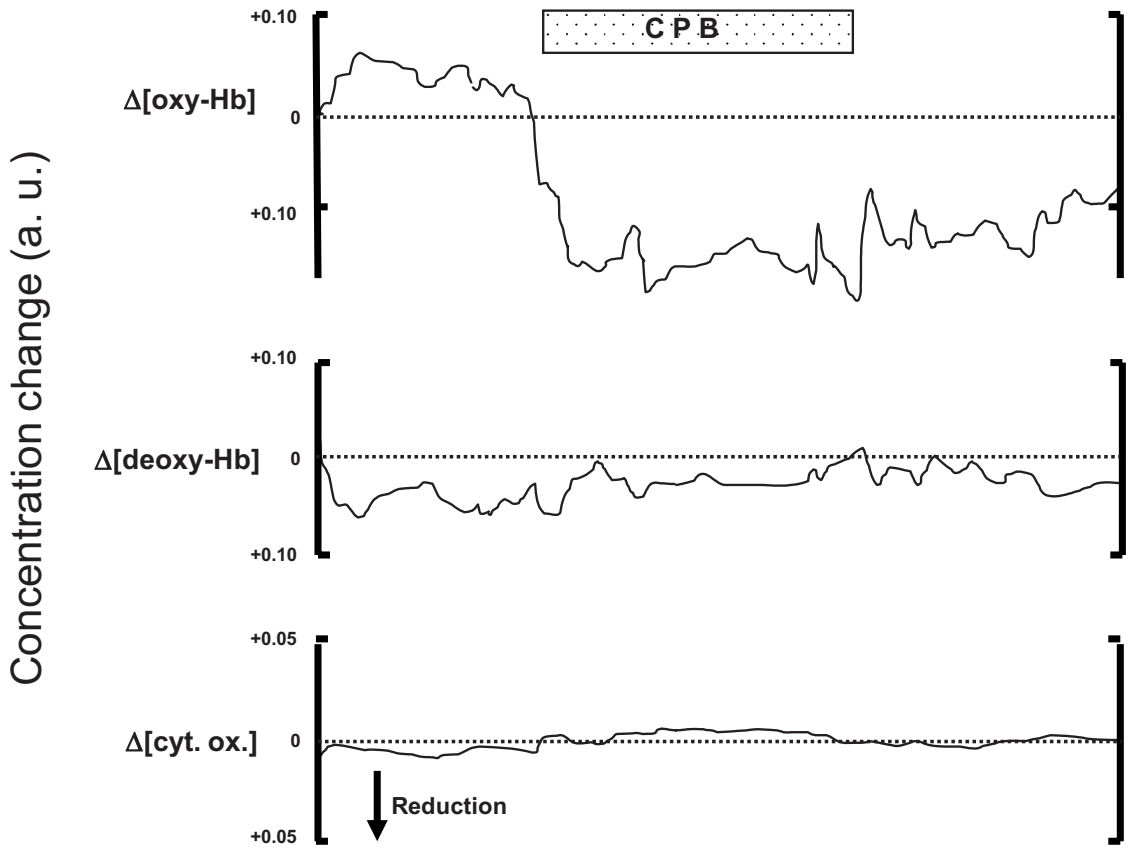

Fig. 7 Changes in [oxy-Hb], [deoxy-Hb], and cytochrome oxidase (measured by NIRS) during cardiopulmonary bypass (CPB) in surgery to repair the descending aorta of a 59-year-old male. The cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) showed a marked and prolonged reduction (type Z), and the redox state of cytochrome oxidase remained at the initial level throughout the operation (type A). Upward deflections indicate an increase in the relative concentrations of [oxy-Hb] and [deoxy-Hb], and oxidation of cytochrome oxidase.

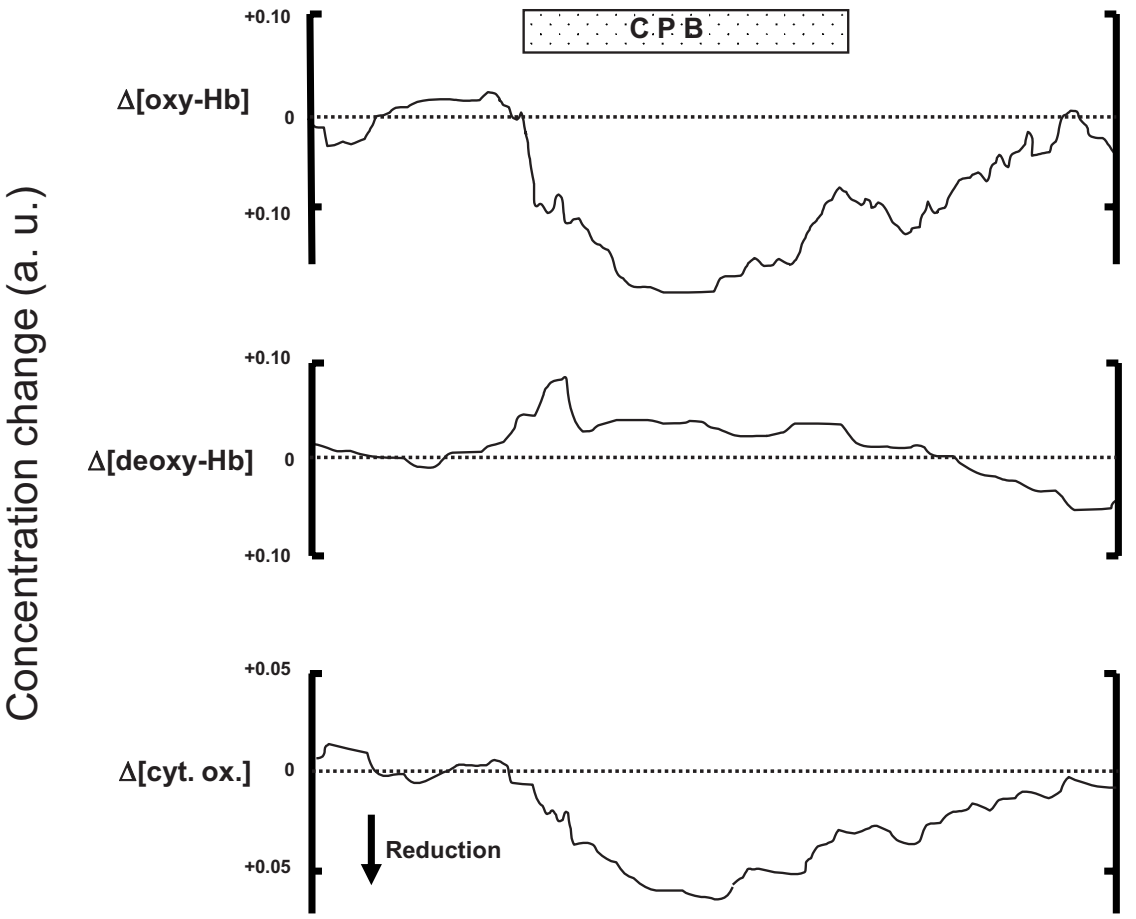

Fig. 8 Changes in [oxy-Hb], [deoxy-Hb], and cytochrome oxidase (measured by NIRS) during cardiopulmonary bypass (CPB) in surgery to repair the ascending aorta of a 74-year-old male. The cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) showed a marked and prolonged increase (type X), while the cytochrome oxidase redox state showed a temporary reduction that returned to the initial level near the end of the operation (type B). Upward deflections indicate an increase in the relative concentrations of [oxy-Hb] and [deoxy-Hb], and oxidation of cytochrome oxidase.

rebral oxygen index at the end of the operation. We cannot explain exactly why the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) by NIRS could not detect the occurrence of a brain injury. However, one of the explanations for them is shown in the following paragraphs.

Figure 10 shows changes in the cerebral oxygenation of patients who had undergone cardiopulmonary resuscitation (CPR) three days prior. When pupil dilation occurred, indicating inadequate blood supply to the midbrain, the value of jugular venous oxygen saturation ($SjvO_2$) was extreme high, and cerebral hemoglobin oxygenation gradually increased; however, the redox state of cytochrome oxidase continued to decline, and the patient was diagnosed as brain dead two days later. Hyperoxia of the internal jugular venous blood has been reported in patients who suffered coma or brain death; this was thought to be because the external carotid regions had received "luxury perfusion," and the absence of filling of intracranial arteries was commonly observed in the patients with brain death, resulting in hyperoxia of the venous blood returning from the extracerebral tissues.[41] Kyttä et al.[42] have reported that high values of $SjvO_2$ in patients who suffered brain death does not always indicate decreases in oxygen extraction in the intracranial brain tissue, and the degree of cerebral tissue hypoxia cannot be judged by near-infrared measurement of hemoglobin oxygenation alone. In the present work, we have shown that there was no significant relationship between the occurrence of severe brain injury and the magnitude of the cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) (Table 2), which was almost the same as that in the case of brain dead patients observed by Kyttä et al. However, our data demonstrate that the redox behavior of cytochrome oxidase (as measured by NIRS) can provide direct, real-time information regarding crises in cerebral oxygen metabolism associated with relatively widespread hypoxia and/or ischemia, and that acquiring such information enables us to both assess the likely degree of cerebral damage and predict the postoperative cerebral outcome (Table 2).[40]

Figure 11 shows a valuable clinical case. An 18-year-old man was involved in a motorcycle accident and underwent emergency surgery for aortic dissection. During surgery [Fig. 11(a)], the patient suffered massive hemorrhage, life-threatening arrhythmia, cardiac arrest, pupil dilation, and a marked reduction in levels of cytochrome oxidase. Open-heart cardiac massage was immediately performed. The heart began to beat again 30 min later, and cytochrome oxidase reoxidation was seen; however, cytochrome oxidase reduction was again detected 1 h later. While monitoring cytochrome oxidase reduction, therapy was actively performed to protect the

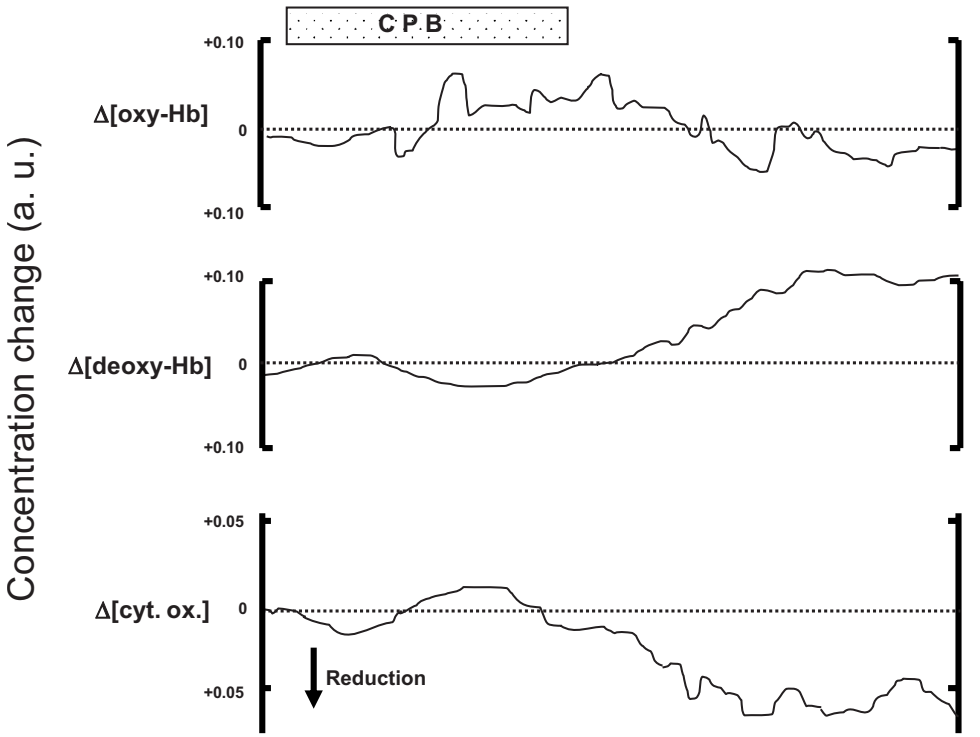

Fig. 9 Changes in [oxy-Hb], [deoxy-Hb], and cytochrome oxidase (measured by NIRS) during cardiopulmonary bypass (CPB) in surgery to repair the aortic arch of a 63-year-old female. The cerebral oxygen index ([oxy-Hb] minus [deoxy-Hb]) showed a marked and prolonged reduction (type Z), while the redox state of cytochrome oxidase showed a marked and prolonged reduction that did not return to the control level during the operation (type C). Upward deflections indicate an increase in the relative concentrations of [oxy-Hb] and [deoxy-Hb], and oxidation of cytochrome oxidase.

Table 1 Characteristics of the nine patients who suffered stroke. CPB is the duration of cardiopulmonary bypass; Ao clamp is the duration of aorta clamping; SCP is the duration of selective cerebral perfusion; Emerg. is emergency; RCI is the regional cerebral infarction; and SAH is subarachnoid hemorrhage.

	Age/Sex	CPB (min)	Ao Clamp. (min)	SCP (min)	Emerg.	Type of Hb/cyt.ox.	Neurological outcome	Post-op CT or MRI
1	66/M	207	151	135		X/A	Blindness	Occipital Cerebellar Infarct.
2	77/M	277	96			X/B	Convulsion	
3	68/M	221	156	187	(E)	Z/B	Hemiplegia	RCI
4	61/M	162	125	35	(E)	Z/B	Hemiplegia	
5	72/M	178	57	84		X/B	Hemiplegia	Watershed infarct.
6	48/F	149	78	65		Z/B	Coma	global in farct. SAH
7	65/M	230	87		(E)	Z/C	Coma	
8	70/F	238	128	169		Y/C	Coma	
9	63/F	332	229	260	(E)	Z/C	Coma	

Table 2 Relationship between occurrence of postoperative brain injury and type of cerebral index ([oxy-Hb] minus [deoxy-Hb]), and cytochrome oxidase behavior observed during surgery.

Oxygenation of Hb ([oxy-Hb]-[deoxyHb])					Redox behavior of cytochrome oxidase				
	Brain Injury					Brain Injury			
	X-type	Y-type	Z-type			A-type	B-type	C-type	
Yes	3	1	5	9	Yes	1	5	3	9
No	22	12	23	57	No	33	24	0	57
	25	13	28	66		34	29	3	66
	P=0.647 chi-square test for independence					P<0.0001 chi-square test for independence			

brain, including mild hypothermia (32°C) and the administration of various drugs (magnesium, steroids, barbiturates, mannitol, glyceol, etc.). Complete oxidation of cytochrome oxidase was achieved several hours after the operation [Fig. 11(b)]. The patient regained consciousness without brain injury. These findings suggest that in cases of severe brain injury (systemic brain ischemia, hypoxia, or cerebral edema), the brain can be resuscitated using active brain protective therapy while monitoring cytochrome oxidase redox. This shows that NIRS represents not only a monitoring technique for detecting brain injury, but also an indicator for assessing therapeutic effects in brain injury.

Lifshitz, Janmey, and McIntosh[43] suggest that mitochondria are maximally swollen at 3 h after brain injury, and scattering decreases and transmission increases may incorporate components of swelling, internal structure modification, and changes in concentration of mitochondria, which can occur simultaneously. Time-resolved spectroscopy (TRS) is a new

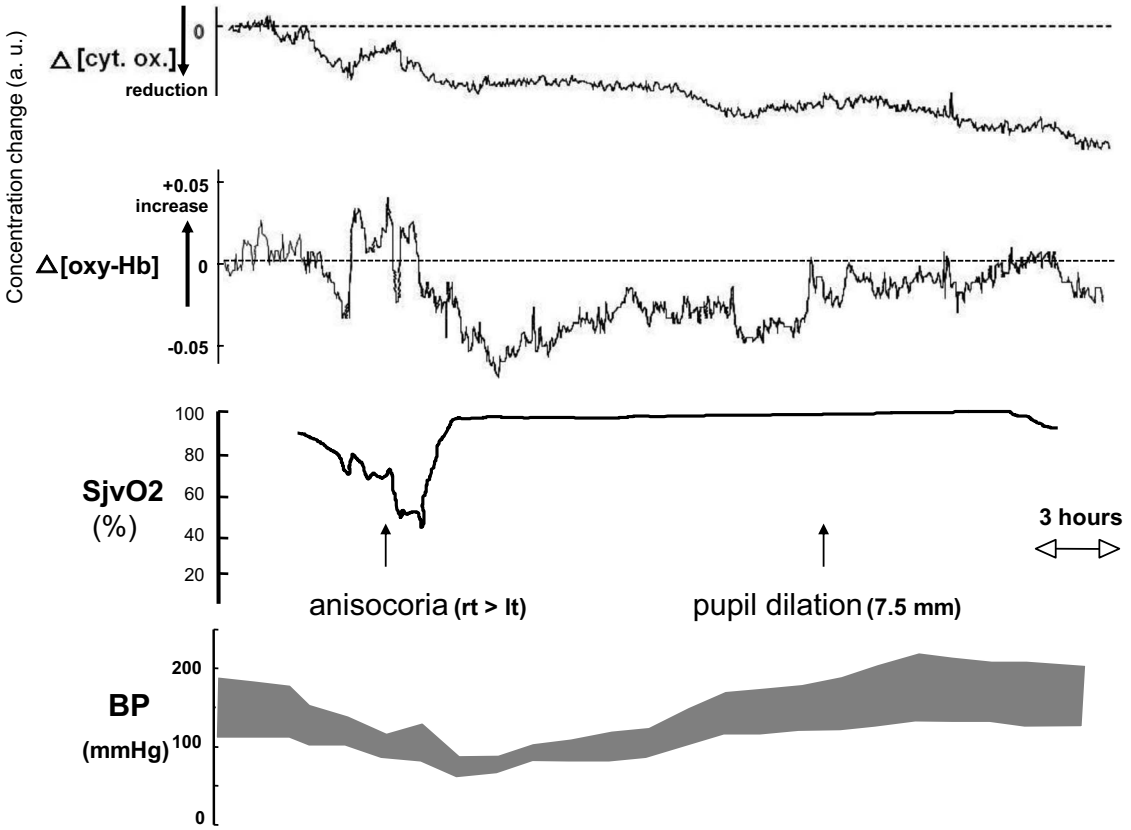

Fig. 10 Changes in cytochrome oxidase, oxy- Hb, $SjvO_2$, and blood pressure in a 43-year-old male who underwent cardiopulmonary resuscitation three days prior, and was diagnosed as brain dead two days later. $SjvO_2$ is jugular venous oxygen saturation; and BP is blood pressure.

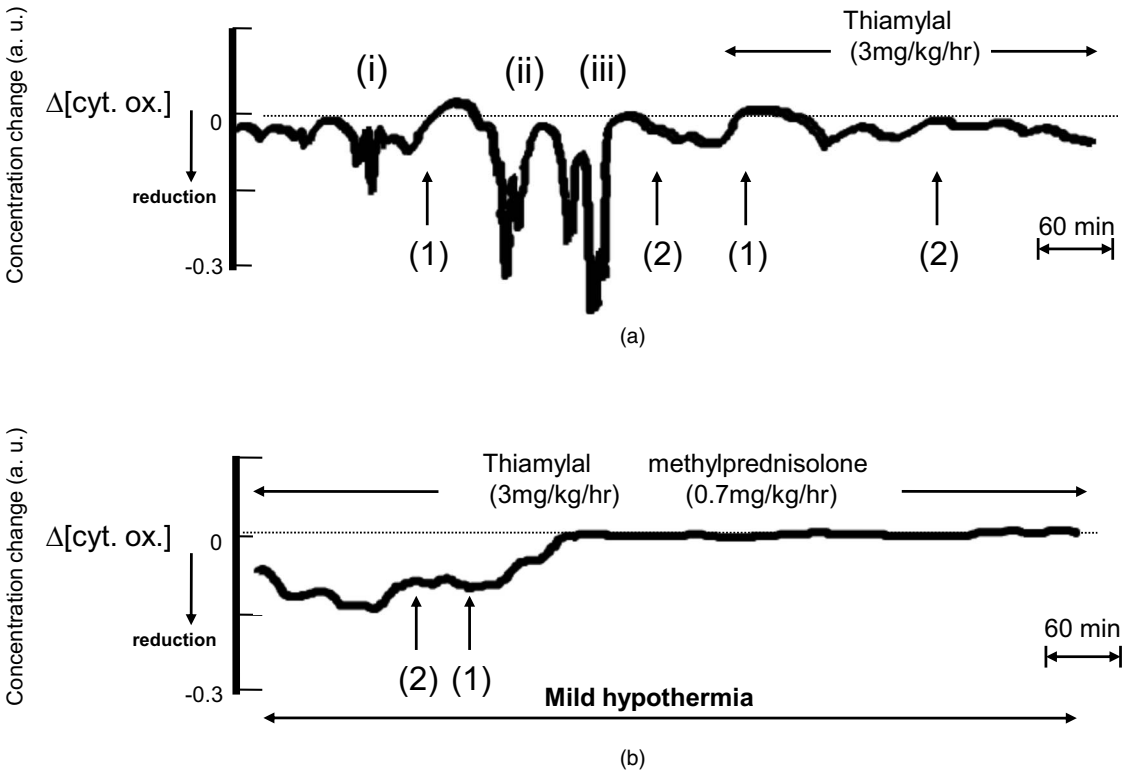

Fig. 11 Changes in the redox state of cytochrome oxidase (a) during and (b) after surgery without cardiopulmonary bypass to repair the descending aorta of an 18-year-old male patient. (i): massive hemorrhage; (ii): ventricular tachycardia and fibrillation; (iii): cardiac arrest; (1): infusion of D-Mannitol (60 g); (2): infusion of glyceol (200 ml); mild hypothermia: body temperature was kept at 32°C.

cerebral monitoring method that measures mean optical path length, and the absorption coefficient (μ_a) and scattering coefficient (μ_s').[44] Since the therapies targeted toward mitochondria have proven beneficial, both histologically and behaviorally, in the recovery from ischemia[45] and trauma,[46] it might be important to monitor not only the redox state of cytochrome oxidase in the mitochondria by a conventional NIRS instrument, but also the scattering properties, which are influenced by swelling and structure modification in the mitochondria, by a TRS instrument.

6 Shortcomings of Near-Infrared Spectroscopy

NIRS has been clinically available for more than a decade, and initially has been given attention as a useful perioperative cerebral monitoring technique for noninvasively detecting intracerebral oxygenation. What are the applications of the currently available forehead-mounted NIRS devices? Central nervous system and psychiatric disorders are more likely to occur following cardiovascular surgery in comparison with other surgeries. Al-Rawi, Smielewski, and Kirkpatrick[47] showed that hemoglobin concentration in the brain calculated by using the modified Beer-Lambert law was significantly affected by extracranial blood flow changes, while tissues oxygen index (TOI) with the use of spatially resolved reflectance spectroscopy reflected intracranial oxygenation (not extracranial changes) with a high degree of sensitivity and specificity. Based on postmortem studies and correlative analysis of intraoperative events with neurologic outcomes, three primary mechanisms appear responsible for brain injury in otherwise uncomplicated cardiac operations: cerebral emboli, cerebral hypoperfusion, and cerebral hypoxia. The causes of these disorders include: 1. macroemboli (i.e., calcific and atheromatous debris) and microemboli (i.e., microgaseous bubbles, platelets, white blood cells, and fibrin agglutination); 2. decreased cerebral blood flow (pump oxygenator-related low flow, low perfusion pressure, hypocapnia, positional abnormality of blood supply/removal of cannulae, carotid artery disease, and cerebrovascular disorders); and 3. cerebral hypoxia induced by hemodynamic disturbance following respiratory failure. Unfortunately, NIRS cannot detect changes in remote areas from the measurement site, making it difficult to detect local brain injuries such as brain embolism using this method. However, forehead NIRS adequately detects changes affecting the entire brain, such as cerebral hypoperfusion or cerebral hypoxia. In particular, it readily enables the detection of medical accidents such as problems with extracorporeal circulation, occlusion of a supply tube used in separate cerebral perfusion, abnormal oxygen supply from an oxygenator, arterial or venous cannulae anomalies related to the use of an artificial pump, artificial respirator malfunctions, and abnormal respiration or circulation. Furthermore, the NIRS equipment setup requires little time, which is important in emergencies. Because cerebral flow correlates to cardiac output in shock,[48] NIRS should be used during shock or resuscitation as a device for monitoring respiration and circulation.

Xiao et al.[49] reported that NIRS can be applied to monitor cerebral blood volume, Hb oxygenation state, cytochrome oxidase redox state, and water content following cardiac

arrest in rats. The data obtained in the present study show that NIRS represents not only a monitoring technique for detecting brain injury, but also an indicator for assessing therapeutic effects following brain injury [Figs. 11(a) and 11(b)]. Because the ultimate goal of resuscitation is social reintegration, noninvasive cerebral monitoring such as NIRS should be performed as soon as possible in brain resuscitation.

Questions have been raised regarding brain oxygenation by NIRS because intraoperative NIRS monitoring is known to have shown no abnormalities in patients who subsequently developed marked postoperative brain injury such as stroke.[40] Many clinicians are therefore skeptical about using NIRS for detecting brain injury. The current commercially available NIRS device is designed to be placed on the forehead; however, it is impossible to detect regional cerebral infarction in areas located far from the monitoring site (i.e., in the occipital lobe, temporal lobe, and basal ganglia), because the light cannot reach these areas. Ideally, if a probe could be placed in six locations (on the left and right of the forehead, temporal lobe, and occipital lobe), then most of the brain (except for the basal ganglia) could be covered, and detection sensitivity would be increased several fold.

In the clinical setting, NIRS signals obtained by blocking the internal carotid artery are clearly greater than those obtained by blocking the external carotid artery.[47] Therefore, a certain percentage of light signals detected by NIRS are assumed to originate from brain tissue; however, many clinicians question the penetration depth of NIRS. A recent study regarding the contribution of different parts of the head to the near-infrared signal revealed that most of the signal attributed to the brain arises from the upper 1 to 2 mm of the cortical surface, for a source–detector separation of 30 mm.[50] These results indicate that the cerebral hemoglobin signal is highly sensitive to hemodynamic changes in the scalp because of the marked contribution of extracerebral tissue; however, changes in the redox state of cytochrome oxidase will be affected primarily by mitochondrial oxygen concentration, and may be less prone to extracerebral contamination because cytochrome oxidase is not present in red blood cells and is present in a lower concentration in the skin compared to that in brain tissue even though under "luxury perfusion," resulting in hyperoxia of the venous blood returning from the extracerebral tissues (Fig. 10).

Numerous systematic review studies tend to report positive results regarding the clinical efficacy of NIRS for cerebral monitoring in cardiac surgery,[51–54] for bedside cerebral blood flow measurements, and for mapping structure and function.[55–57] However, most of these studies have major methodological limitations and low levels of evidence. Therefore, further investigations, such as multicenter randomized controlled trials, are clearly required to determine the clinical significance of cerebral monitoring (cerebral hemoglobin oxygenation and redox state of cytochrome oxidase) by NIRS.

7 Conclusions

We apply NIRS to both animal and clinical investigations. Based on these results, we discuss the significance of the measurement of cerebral hemoglobin oxygenation and cerebral cytochrome oxidase *in vivo* and in the clinical setting. From our data, we conclude that the redox behavior of cytochrome oxidase during surgery is likely to be a good predictor of the postoperative cerebral outcome. Our data indicate that although changes in local regions located far from the monitoring site may escape detection, the oxygen sufficiency or deficiency of brain tissue on a more global scale can be evaluated by near-infrared measurement. We are now sufficiently confident of its reliability to alter our strategy if the NIRS data indicate that the patient is experiencing deficient cerebral oxygenation; however, further investigation is required to establish its clinical efficacy and justify its routine use during operative and perioperative periods.

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