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Effects of Hemoglobin Concentration, Skull Thickness, and the Area of the Cerebrospinal Fluid Layer on Near-infrared Spectroscopy Measurements

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Background: **Previous studies documented that near-infrared spectroscopy values were affected by factors related to optical path length, such as hemoglobin concentration, the differential path length factor, skull thickness (t-skull), and the area of the cerebrospinal fluid layer (a-CSFL). Lately, the NIRO-100 (Hamamatsu Photonics, Hamamatsu, Japan) has provided a tissue oxygen index (TOI) that theoretically is not supposed to be affected by optical path length. Therefore, the authors hypothesized that TOI is not influenced by the above-described individual factors.**

Methods: **Cardiac surgical or neurosurgical 103 patients (65 men and 39 women; aged 63 ± 14 yr) were studied. TOI and regional cerebral oxygen saturation (rSO_2) (INVOS 4100; Somanetics, Troy, MI) were measured sequentially on patients in a resting state. The t-skull and a-CSFL were calculated using computed tomographic image slices of the head corresponding with the position of near-infrared spectroscopy sensors. The effects of these two factors, hemoglobin concentration and mean arterial pressure, on TOI and rSO_2 values were evaluated by linear regression analysis.**

Results: **Simple linear regression analysis showed that mean arterial pressure ($r = 0.27$, $P = 0.008$), t-skull ($r = 0.22$, $P = 0.034$), a-CSFL (0.26, $P = 0.012$), and hemoglobin concentration ($r = 0.42$, $P < 0.0001$) were significant determinants of rSO_2. Multiple linear regression analysis showed that hemoglobin concentration ($r = 0.34$, $P < 0.001$), a-CSFL ($r = -0.252$, $P = 0.012$), and t-skull ($r = 0.22$, $P = 0.037$) were significant determinants of rSO_2. On the other hand, simple and multiple linear regression analysis showed that there was no significant determinant of TOI.**

Conclusion: **rSO_2 values were affected by hemoglobin concentration, a-CSFL, and t-skull, but TOI values were not affected by individual factors.**

CEREBRAL oxyhemoglobin concentrations measured by near-infrared spectroscopy (NIRS) have been clinically used as a noninvasive and continuous monitor. There was a good correlation between NIRS values and cerebral blood flow velocity by transcranial Doppler in evaluating cerebral vasomotor reactivity.[1–3] Further NIRS measurements demonstrated its usefulness to evaluate the cerebral oxygen balance during cardiopulmonary bypass as an index of cerebral injury.[4,5] NIRS measurement has such great advantages, but there has been no gold standard as to its absolute value.[6] NIRS measurement could only report a change from a baseline.[7,8] Previous studies documented that NIRS values were affected by various factors such as hemoglobin concentration,[9,10] the differential path length factor,[11] extracranial blood contamination,[12,13] skull thickness, and the area of cerebrospinal fluid (CSF) layer.[14] To reveal these effects on the NIRS values is an urgent issue for establishing accurate cerebral monitoring methodology.

A modified Beer-Lambert law has been used to calculate cerebral hemoglobin concentration by NIRS. In the modified Beer-Lambert law, optical path length is one of the most important factors to calculate NIRS values[11] and is related to hemoglobin concentration, skull thickness, and the cerebrospinal fluid layer. Recently introduced, the tissue oxygen index (TOI) derived from NIRS monitor, NIRO-100 (Hamamatsu Photonics, Hamamatsu, Japan), is one of the absolute cerebral oxygen saturation. The NIRO-100 uses a spatially resolved spectroscopy (SRS) methodology and two unique, closely spaced detectors to measure light attenuation as a function of source-detector separation, which is theoretically not supposed to be affected by the optical path length.[15] However, to date, the effects of each factor such as hemoglobin concentrations, skull thickness, and the area of the CSF layer on TOI values have not been tested clinically. There are only computer simulations (Monte Carlo simulation) that test whether superficial tissue thickness or skull thickness and the area of CSF layer have an effect on NIRS values.[14]

Instead of computer simulation,[14,16] computed tomographic (CT) images of the head enable quantification of skull thickness, and the area of the CSF layer where the space is occupied by cerebrospinal fluid. Therefore, we conducted the study to investigate whether TOI is influenced by the above-described individual factors by using the CT scan slice of the head corresponding to the position of the NIRS sensor. We also tested the effects of the above factors on regional cerebral oxygen saturation (rSO_2) derived from INVOS 4100 (Somanetics, Troy, MI), which is one of the most frequently used NIRS values consequently.

Materials and Methods

Patients

After institutional approval and informed consent, we prospectively recruited 105 patients with CT images of

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the head from the National Cardiovascular Center (Suita, Osaka, Japan) in this study. All patients had the CT scan examination for screening for preoperative evaluation or for evaluation of their cerebral disease symptoms. In the case that there was an interval of more than 14 days between NIRS measurement and CT examination, patients were excluded. The patients with redness or rash on their forehead were also excluded from this study.

NIRS Apparatuses

Cerebral oxygen saturation, regional cerebral oxygen saturation (rSO_2), and tissue oxygen index (TOI) were measured using INVOS 4100 and NIRO 100, respectively. INVOS 4100 uses two wavelengths of near-infrared light (730 and 810 nm) and measures the ratio of oxyhemoglobin to total hemoglobin, which is a percentage value, rSO_2. The sensor is composed of a light-emitting diode and two detectors located 30 and 40 mm from the light-emitting diode, allowing for the removal of the extracranial contribution of scattered light by the application of a subtraction algorithm. The proximal detector receives a signal from the shallower part of the brain, whereas the distal detector measures the saturation of all of the tissue, including skin, muscle tissue, skull, and the brain. If the signal detected by the proximal detector is subtracted from that of the distal detector, the ratio of oxyhemoglobin concentration and total hemoglobin concentration can give a mean value for cerebral saturation. The NIRO-100 monitor uses three wavelengths of near-infrared light (775, 825, and 850 nm), and the sensor contains a laser diode and two detectors placed at 3.7 or 4.3 cm from the source of emitting light. It can measure a TOI (%), which is the ratio of oxyhemoglobin to total hemoglobin. NIRO-100 uses the SRS method, which combines the multidistance measurements of optical attenuation and makes it possible to calculate the concentration of oxyhemoglobin and deoxyhemoglobin in the tissue. Therefore, the TOI (%) can be rapidly calculated.[17] In contrast to the modified Beer-Lambert equation, the values derived by SRS are not affected by differential path length factors.

NIRS Measurement

After having a patient keep a supine position on the bed for more than 5 min, we measured cerebral oxygen saturation by INVOS 4100 and NIRO 100. For the measurements, the cerebral oximeter probe was placed on the right forehead, with the caudal border approximately 1 cm above the eyebrow and the medial edge at the midline. This places the light source and sensors away from the frontal sinus. After the measurement of INVOS 4100, we placed the emitter of NIRO 100 at the same place as the emitter of INVOS 4100. Simultaneously, mean arterial pressure and pulse oximetry were measured noninvasively by a portable patient monitor M3 (Philips, Andover, MA). Blood samples were also taken for measurements of blood hemoglobin concentration.

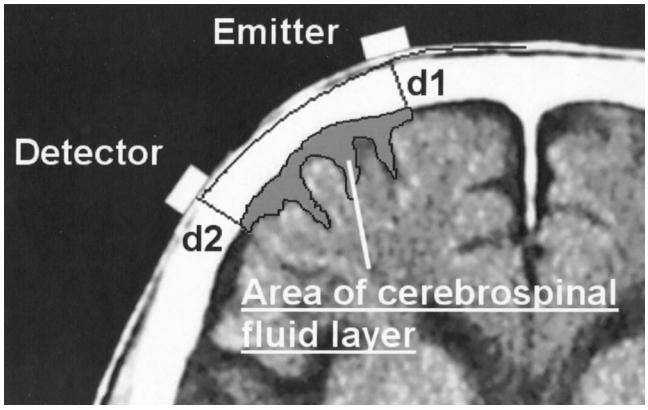

Fig. 1. The schema of calculating skull thickness and the area of cerebrospinal fluid layer. The skull thickness, d1 and d2, was measured at the position of emitter or detector perpendicularly. The area of cerebrospinal fluid was traced and measured by NIH ImageJ for Windows (National Institutes of Health, Bethesda, MD).

Calculating Parameters from CT Image

We calculated the skull thickness from where optical emitter or detector was placed (fig. 1, at d1 and d2) and the areas of the CSF layer were measured as figure 1 to estimate the effects of them on cerebral oxygen saturations. The CT scan slice of the head corresponded with the position of the sensor. The area of the CSF layer was calculated by NIH ImageJ version 1.2 for Windows (National Institutes of Health, Bethesda, MD). After tracing the CSF layer between the emitter and detector in handwriting, NIH ImageJ could calculate the traced area (fig. 1).

Statistical Analysis

The effects of skull thickness, the area of the CSF layer, blood hemoglobin concentration, and mean arterial pressure on rSO_2 and TOI values were evaluated by simple and step-up multiple linear regression analysis with SPSS version 11 (SPSS Inc., Chicago, IL). Also, the relation between rSO_2 and TOI was analyzed by the Pearson correlation coefficient with the level of significance at 0.05. Agreement between the two methods was examined by the statistical method described by Bland and Altman.

Results

Baseline Characteristic of Patients

Of the enrolled 105 patients, 2 patients were excluded for their redness of forehead. Patient characteristics are shown in table 1. Measured parameters are also shown in table 2.

Significant Factors of rSO_2 and TOI

Values of hemoglobin concentrations, mean arterial pressure, skull thickness, and the area of the CSF layer

Table 1. Patients' Characteristics (n = 103)

Brain disease (n = 54)	Aneurysm	27
	Ischemic cerebral disease	23
	Hydrocephalia	4
Heart disease (n = 49)	Ischemic heart disease	11
	Valve disease	6
	Great artery disease	32

are shown in table 3. All of these factors were significant determinants of rSO_2 values, but not of TOI by single regression analysis. Multiple regression analysis showed that hemoglobin concentration, skull thickness, and the area of the CSF layer were significant determinants of rSO_2 (table 4). In regard to TOI, no significant factors were selected by step-up procedure.

Relation between rSO_2 and TOI

There was a significant correlation between rSO_2 and TOI as shown in figure 2A ($r = 0.41$, $P < 0.0001$). However, Bland and Altman analysis demonstrated that there was a wide limit of agreement (bias was 7.2% and precision was 18.9%; fig. 2B).

Discussion

In this study, it was demonstrated that hemoglobin concentration, skull thickness, and the area of CSF layer had effects on rSO_2 values, but not on TOI. Although there was a weak correlation between rSO_2 and TOI, Bland and Altman analysis revealed a wide limit of agreement between the two values.

Our previous reports[9,10] demonstrated that rSO_2 values were dependent on hemoglobin concentration, and the results of this study were compatible with those. As hemoglobin concentration decreased, rSO_2 values also decreased. Optical path length, which means how far near-infrared light can travel through tissue, is one of the most important factors to measure NIRS values. Kurth *et al.*[18] indicated that there was a negative correlation between the optical path length and hemoglobin concentration. A reduction of hemoglobin concentration leads to an increase in optical path length because the ratio of an attenuation of near-infrared light intensity decreases. An absorbance of the near-infrared light by chromosomes in hemoglobin decreases. The modified Lambert Beer law that has been used for calculation of NIRS measurements includes the optical path length in its formula as a constant. Therefore, the change of the optical path length that should be constant would cause the discrepancy between a real NIRS value and the measured NIRS value. Lassnigg *et al.*[19] suggested that there could be an overestimation of NIRS measurement under hemodilution during cardiopulmonary bypass. It was not clear whether this mechanism caused the overestimation of NIRS measurement because the algorithms INVOS uses were not opened. There was a strong correlation between NIRS values and hemoglobin concentration in this study. That should be taken into account to evaluate cerebral oxygenation with NIRS values.

Young *et al.*[20] reported that the NIRS measurement also depended on skull thickness. The authors fixed the emitter on the skin and moved the detector from the skin to bone, dura, and cerebral cortex sequentially. The light intensity that the detector could receive decreased dramatically when the detector was put down on the skull or dura mater. Most of the near-infrared lights were scattered or reflected before they reached to the cerebral cortex. Further, Okada *et al.*[14] indicated that superficial tissue and cerebrospinal fluid thickness had a significant effect on the intensity of the detected light. The thicker the skull or CSF layer is, the less near-infrared light can be detected. That would make rSO_2 values lower.

On the other hand, TOI values were not affected by those factors such as skull thickness, the area of the CSF layer, and hemoglobin concentration. One reason is that the algorithm of TOI does not include optical path length in the formula. In addition, the SRS algorithm is based on the following assumptions: The geometry of tissue is a semi-infinite half-space, and the wavelength

Table 2. Patients' Basic Data (n = 103)

Age, yr	63 ± 14
rSO_2, %	58 ± 10
TOI, %	65 ± 7
Hemoglobin concentration, g/dl	12.9 ± 2.0
MAP, mmHg	91 ± 13
Skull thickness, cm	1.99 ± 0.32
Area of cerebrospinal fluid layer, cm^2	0.52 ± 0.43

Data are expressed as mean ± SD.

MAP = mean arterial pressure; rSO_2 = regional cerebral oxygen saturation; TOI = tissue oxygen index.

Table 3. Results of Single Regression Analysis

	rSO_2		TOI	
	R	*P* Value	*R*	*P* Value
Hemoglobin concentration	0.42	< 0.0001	0.13	0.187
MAP	0.27	0.008	0.05	0.626
Skull thickness	0.22	0.034	0.15	0.150
Area of cerebrospinal fluid layer	−0.26	0.012	0.11	0.290

MAP = mean arterial pressure; rSO_2 = regional cerebral oxygen saturation; TOI = tissue oxygen index.

Table 4. Results of Multiple Regression Analysis

Significant Factors	Multiple Regression Coefficient	Standardized Coefficient	*P* Value
	0.487		< 0.001
Hemoglobin concentration		0.335	< 0.001
Area of cerebrospinal fluid layer		−0.252	0.012
Skull thickness		0.220	0.037

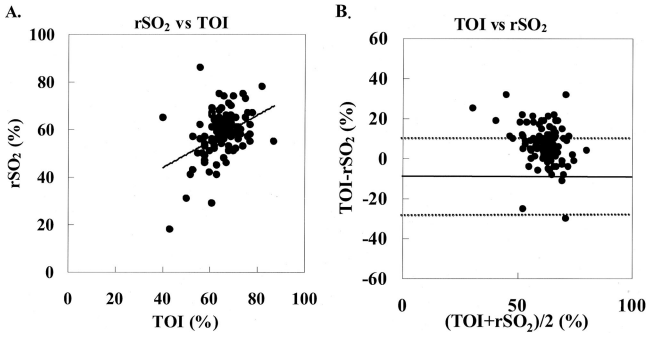

Fig. 2. (*A*) The relation between regional cerebral oxygen saturation (rSO_2) and tissue oxygen index (TOI) with linear correlation analysis. (*B*) Bland and Altman analysis with individual values of rSO_2 and TOI. *Upper* and *lower dotted horizontal lines* correspond to ±1.96 SD.

dependence of scattering coefficient of tissue is known. In TOI measurement, the scattering coefficient is unknown and supposed to be constant, but actual brain tissue including the skull and CSF layer is not a semi-infinite half-space. The change of hemoglobin concentration cannot affect the scattering coefficient, but the variation of the skull thickness or the area of CSF layer in patients could cause a change in the scattering coefficient. Although both oxyhemoglobin and deoxyhemoglobin include the scattering coefficient, in calculating TOI, oxyhemoglobin is divided by total hemoglobin (oxyhemoglobin + deoxyhemoglobin), and scattering coefficients are canceled finally. Therefore, TOI could not be affected by individual variation.

Furthermore, the TOI had enough sensitivity to detect vasomotor reactivity during carbon dioxide or hypoxic challenge.[21–23] Previous studies also demonstrated that a reduction of TOI was associated with brain injury or lower cerebral perfusion in cardiopulmonary bypass. During deep hypothermic circulatory arrest, TOI less than 55% was associated with cerebral tissue damage.[4] In a piglet pediatric cardiac surgery model, only TOI could detect the lower cerebral blood flow after superior vena cava cannula obstruction.[24] TOI is not only affected by hemoglobin concentrations, skull thickness, and the area of the CBF layer, but also has clinical relevancy. To date, a number of efforts have been made to exclude various contaminations from NIRS measurements. Regarding hemoglobin concentration, there is room for discussion, because a reduction of hemoglobin concentration could cause a decrease of oxygen delivery. However, the effects of skull thickness or the area of CSF layer on NIRS measurement should be excluded to acquire the validity of the absolute NIRS values.

Various approaches have been tested to solve the issue of data quantification of NIRS measurement. Available commercialized NIRS apparatuses use time-resolved spectroscopy,[25,26] phase-resolved spectroscopy,[27] and SRS.[17] Time-resolved spectroscopy and phase-resolved spectroscopy are the most reliable methods of NIRS measurement because they can measure the optical path lengths directly. However, the machines need a lot of space, are delicate to operate, and cost much. Therefore, most commercially available machines use SRS or other algorithms. Although TOI using SRS has some advantages compared with rSO_2, the reliability of TOI as an absolute value still remains to be determined. The most important issue is that the brain does not have a uniform structure, not like a phantom to calibrate NIRS measurements. Some errors are inevitable because the brain is supposed to be uniform in the calculation algorithms. To pursue more accurate NIRS analysis, frequency domain NIRS has been developed. This method combines phase-resolved spectroscopy and SRS to estimate the absorption and scattering coefficient.[28,29] Although the frequency domain NIRS may have an advantage, the ability to calculate the optical path length directly, we should take into account the unsolved assumption.

There were several limitations in this study. First, the patients were, in large part, those who were admitted to the cardiac surgery or neurosurgery ward, not including healthy control patients. However, patients in the cardiac surgery ward had an almost normal image of the head CT scan as commented by radiologists. In a resting state, there could be no serious hemodynamic impairment in those patients. Therefore, most of the patients in the cardiac surgery ward who received no particular comment from radiologists might be suitable for the control group. Second, we could not evaluate the effect of superficial tissue thickness on TOI and rSO_2. The superficial tissue attenuated the intensity of near-infrared light that reached to the sensor[20] and was the potential factor that changed the differential path length factor.[25] The accurate measurement of superficial tissue thickness needs magnetic resonance images of the head. The cost of magnetic resonance images prevented us from performing magnetic resonance image examinations in this study. However, INVOS uses the subtraction method to diminish the effect of the superficial tissue layer in calculating rSO_2. The superficial tissue thickness might have an effect on NIRS values. It is an important issue that should be investigated in a future study. Third, NIRS measurements were performed with patients in an awake state. In a case in which the patients were excited or nervous, that might have had an effect on NIRS values. We took enough time to prevent the patients from being excited or nervous by waiting until blood pressure or heart rate settled to normal ranges in the NIRS measurement.

In summary, we evaluated the degree of the effects of skull thickness, the area of the CSF layer, hemoglobin concentration, and mean arterial pressure on NIRS values clinically, not by computer simulation. rSO_2 values were affected by skull thickness and the area of the CSF layer and hemoglobin concentration compared with TOI.

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