Comparison of cerebral oxygen saturation in premature infants by near-infrared spatially resolved spectroscopy: observations on probe-dependent bias

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Abstract. Spatially resolved spectroscopy (SRS) allows the estimation of absolute tissue oxygen saturation, the ratio of oxygenated to total hemoglobin concentration, which may facilitate the comparison of results among patients. Eighty-two premature infants were included over two years. The cerebral tissue oxygenation index (c-TOI) was measured using NIRO 300 (Hamamatsu Photonics KK). c-TOI was measured at several positions in each infant. c-TOI varied over time, increasing in the first third and decreasing in the last third of the study period ($p<10^{-6}$). Two probes were used in the study, and a highly significant difference was found between these ($p<10^{-6}$). The mean difference was 8.5% (95%CI 5.4 to 11.6%). After correction for this difference, there was no variation over time. A conclusive explanation for the bias could not be identified. Since the study groups were well distributed, the bias had no influence on the results of our clinical study. We investigated an unexpected but highly significant probe-dependent bias in c-TOI with no conclusive explanation. Hence, comparisons of absolute TOI between groups of patients and among studies should be regarded with caution. A better strategy to detect potential instrumental problems will be useful in preventing biased c-TOI from occurring.
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Keywords: near-infrared spectrosopy (NIRS); spatially resolved spectroscopy (SRS); tissue oxygenation index (TOI); newborn; preterm.

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1 Introduction

Conventional near-infrared spectroscopy (NIRS) measures concentration changes in oxygenated, deoxygenated, and total tissue hemoglobin. Spatially resolved spectroscopy (SRS) was introduced to provide an absolute measure of tissue oxygenation that can be measured at the bedside in addition to concentration changes.[1] In the tissue, light is attenuated by both scattering and absorption. In a homogenous medium, attenuation increases with the emitter detector spacing. It has previously been shown that the SRS methodology can exploit the attenuation change over a distance, i.e., the attenuation slope, to estimate a scaled absorption coefficient of the medium.[1] The NIRS monitor adopted in this study (NIRO 300, Hamamatsu Photonics KK) uses three closely spaced detectors to measure the attenuation slope over the tissue. When the underlying absorption coefficient is higher, a larger attenuation slope will be resulted. The scaled absorption coefficients at multiple wavelengths can then be converted into scaled oxy- and deoxy hemoglobin concentrations, i.e., $k\times[O_2Hb]$ and $k\times[HHb]$, where k is an unknown scaling factor accounting for scattering. The tissue oxygenation index (TOI) is calculated as $k\times[O_2Hb]/(k\times[O_2Hb]+k\times[HHb])\times 100\%$. It is noted that the scaling factor k has been cancelled out and will not influence the value of TOI in theory. The TOI can be interpreted as the percentage of oxygenated blood in tissue and is an absolute measure with a numerical saturation value ranging from 0 to 100%.

In theory, the TOI ratio represents all vessels; however, NIRS is particularly sensitive to the small blood vessels. Tissue oxygen saturation is influenced more by venous oxygen saturation than by arterial oxygen saturation, simply because there is more blood in the venous compartment of the circulation. Therefore, it should reflect oxygen extraction and the balance between organ blood flow and demands. Hence, it will be very useful to have a tissue oxygen saturation that can be compared within the same patient at different times, or among patients both in the same or in different groups.

NIRS is particularly suitable for the brain of the premature infant, because of the thin skull and scalp. Monitoring of cerebral oxygen saturation could be valuable in premature infants at risk of hypoxic-ischemic brain damage.[2] This is particular relevant since brain injury and neurodevelopmental deficit is common in this population. We have previously

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shown that the precision of a single measurement using a particular NIRS monitor (NIRO 300, Hamamatsu Photonics KK) was 5.2%, with a spontaneous 2-s variation of 2.9%, in a group of premature infants.[3]

This short communication reports an unexplained systematic variation in cerebral TOI (c-TOI) measured over a two-year period, which was identified during the final data analysis of a clinical study and was possibly due to the use of two different probes.

2 Materials and Methods

Eighty-two premature infants with a gestational age (GA) below 33 weeks were included in a clinical study of the influence of fetal inflammation on cerebral oxygen saturation, at the National University Hospital, Rigshospitalet, Copenhagen, between August 2004 and December 2006. The Danish Ethical Committee [Journal No. (KF) 01-116.04] approved the project, and informed parental consent was obtained in all cases.

The NIRO 300 NIRS monitor (Hamamatsu Phototonics KK, Hamamatsu City, Japan) was used. This NIRS monitor uses a detection probe consisting of one emitter and three detectors at four wavelengths (775, 810, 847, and 919 nm). The emitter and the detector were fixed in a nontransparent, soft probe holder. The distance between the emitter and the detectors was 4 cm. The calibration procedure was performed before start and after each optode positioning, and repeated if measurement failed.

The probe holder was placed in the frontotemporal or frontoparietal region depending on the head size and curvatures. The head size of the infants varied considerably (birth weight 520 to 2590 g). When placing the probe, the part of the head with less curvature was used so that the assumption of a flat geometry in SRS was fulfilled as much as possible. The probe was placed as frontally as possible to reduce the effect of hair. The probe holder was held in position by hand. The NIRS monitor was initialized. Recording was continued until a period of stable signal tracing was achieved. The probe was then replaced several times depending on the head size and the clinical condition of the infant. The NIRS monitor was reinitialized after each replacement before the next measurement. Only the measurements with instrumental warnings of insufficient signal quality were excluded. In this situation, the probe was removed and replaced, the NIRS monitor was initialized, and c-TOI was measured again. One person (L.C.S) did all measurements. The signal was sampled every two seconds. Data were stored on a computer disk for subsequent analysis. For further discussion of the method, please refer to Sorensen and Greisen.[3]

In the study, two different probes were used. Detection probe I was used in the first 20 infants. Since a part of the sealing between the housing and the detector loosened, detection probe I was replaced by detection probe II. There were no warning messages during calibration, and the recorded data looked normal, but to prevent the ingress of moisture, probe I was repaired. Detection probe II was used without any problems until May 2006, when the NIRS monitor encountered problems with the degradation of the electric shielding. The repaired detection probe I then replaced detection probe II and was used until it failed with the same electrical shielding problem. Before and after measurements on a new infant, the detection probes and cables were wiped with a spirit-dampened cloth as recommended by the manufacturer to maintain antiseptic standards for clinical neonatal use. Both probes have subsequently been examined by the manufacturer and found functioning normally, except for the degraded electrical shielding that precludes measurements on patients.

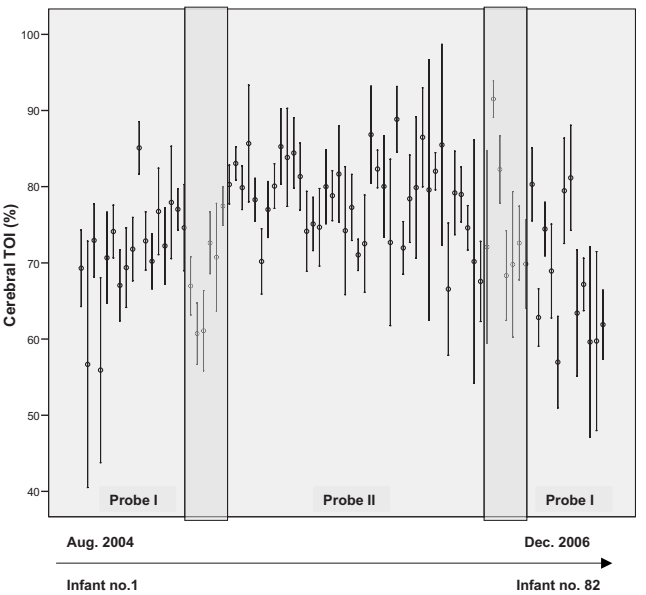

Fig. 1 c-TOI in 82 premature infants. Multiple measurements were made in each infant, and the vertical bars indicate the 95% confidence intervals of individual means. The translucent areas represent the excluded infants. c-TOI varied over time, increasing in the first third and decreasing in the last third of the study period (second-order polynomial regression: $p<10^{-6}$).

We also investigated the possibility of biases introduced by parameter discrepancies (instrumental tolerance) of the detection probe, such as the discrepancies between the supposed and the actual (1) source detector spacing, (2) distances among the three detectors, and (3) sensitivities in the detectors. The investigation was performed through computer simulations using an analytical model based on a semi-infinite homogenous geometry to predict optical attenuation at different detection points from which attenuation slopes were calculated.[4] Using these predicted attenuation slopes, the TOI algorithm (same as the one used by the manufacturer) was used to derive the c-TOI.[1] In order to assess the bias in c-TOI, the three parameters mentioned earlier were changed from their nominal values individually in the simulations.

3 Statistics

c-TOI was plotted as a function of the infant number. Consecutive numbers from 1 to 82 were given in the order the infants were included (Fig. 1). Unexpectedly, mean c-TOI in each infant varied over time, with c-TOI increasing at the beginning and decreasing at the end of the study period (Fig. 1). Weighted polynomial regression was used to examine the significance of this finding. Weighting was made to compensate for the multiple and uneven number of measurements in each infant.

The precise date for probe changes was not known. Approximate dates were worked out. To avoid error, we excluded measurements made from one month before to one month after these dates ($n=14$; corresponding to the translucent areas in Fig. 1). The estimate of probe-dependent bias was based on the remaining 68 infants. Weighted ANOVA with Bon Ferroni's *post hoc* correction showed no significant difference between detection probe I before and after repairing, but significant differences to detection probe II. The level of c-TOI for detection probes I and II was then compared with weighted ANOVA. Correction for probe-dependent bias was done with weighted polynomial regression with the residuals of TOI as dependent variables. $p<0.05$ was considered statistically significant. All results were analyzed with SPSS 12.0 for Microsoft Windows.

4 Results

Eighty-two infants were examined on the first day of life. The median gestational age was 28.9 gestational weeks (23.1–32.7) and median birth weight 1178 g (520–2590). The median number of TOI measurements on each infant was 6 (3–11).

TOI was measured 518 times in total. c-TOI varied over time with increasing values at the beginning and decreasing values at the end of our study period (Fig. 1). This correlation was highly statistically significant ($p<10^{-6}$).

Detection probe I was used in 29 infants, and detection probe II was used in 39 infants. There was a significant difference in c-TOI between the two probes: mean c-TOI =70.4% (95%CI 65.2 to 75.5) versus mean c-TOI=78.8 (95%CI 76.8 to 80.9) ($p<10^{-6}$), probe I and II, respectively. The mean difference was 8.5% (95%CI 5.4 to 11.6%). When adjusting for probe-dependent bias, there was no significant variation over time.

No changes in subject inclusion criteria or NIRS protocol were made over the two-year period, and there were no associations between the many clinical variables and probe number. There were no associations to time of day or year. Infants with fetal inflammation were randomly distributed.

Our computer simulations showed that the amount of bias caused by parameter discrepancies changes with the real underlying c-TOI. For real c-TOI in the range between 60% and 80%, the maximum bias caused by the discrepancies between the supposed and the actual (1) source detector spacing, (2) distances among the three detectors, and (3) sensitivities in the detectors in the normal range was below 1%. This showed that the TOI algorithm is reasonably robust to parameter discrepancies in the normal range and cannot explain the c-TOI bias observed in this study.

5 Discussion

This manuscript reports an unexplained systematic bias in TOI using the NIRO 300 monitor. Obviously, this problem cannot be generalized to involve other NIRS instruments or NIRS in general. TOI has been shown to be useful in trend monitoring in the same patient in many different clinical situations, for example, cardiopulmonary bypass surgery. While the main application of TOI is monitoring arbitrary changes of tissue chromophores, we investigated the use of TOI as an absolute measure for comparing cerebral oxygenation among different infants that, if proved feasible, would allow clinical comparison studies. TOI can in principle provide an absolute measure of tissue oxygenation. While TOI as an absolute measure has been validated in *in vitro* experiments involving homogenous medium,[1] its accuracy in monitoring cerebral oxygen saturation in patients is more difficult to validate because of a lack of gold standard measurements for comparisons. From a theoretical point of view, TOI was derived assuming the measurement site to be a homogenous medium, which is obviously a simplification of the reality. Any inhomogeneities such as the underlying structures of the scalp and brain will affect the numerical value of TOI. It is therefore not surprising to find different c-TOI values for different measurement sites on a subject's head even when the underlying cerebral oxygen saturation is supposed to be the same. In our previous study,[3] we showed that the within-infant variation was 5.2% when the optical probe was placed at different sites on infants' heads. In this paper, we reported that a bias was found in c-TOI as measured by two different probes.

Several factors can potentially cause such a bias in c-TOI. To allow several measurements at different positions, the probe holder was held in position by hand, rather than by fixing bandage, which would have been more stressful for the infants. Only one person did all measurements (L.C.S.). It may be argued that variation in the applied pressure can influence the measurements, and it cannot be entirely excluded that the operator was initially afraid of exerting pressure on the probe, but with increasing confidence increased the pressure later; and noticing pressure marks at a later stage, decreased the pressure again. To this end, L.C.S. felt confident that consistent pressure had been applied throughout the two-year period, and it is difficult to imagine that such a process took two-years and the study of over 80 infants to complete.

Neither the manufacturer nor we were able to identify any difference between the two optodes in terms of functioning. The calibration procedure of the NIRO 300 was performed before starting measurements; after each single measurement, when the probes where replaced; and repeated, if TOI measurements were unsuccessful. The calibration optimized the power of the light source and checked the normal operation of the three detectors. It is conceivable that under certain conditions, factors that might bias the TOI may not be properly identified by the NIRS monitor itself during the calibration. For example, suppose that the detector closest to the light source is intact but that the housing of the other two detectors is scratched or covered with a small amount of dirt or a small gap exists between the housing and the two detectors. In this situation, the amount of light received by these two detectors will be lower than usual and will lead to a higher attenuation slope as measured by the three detectors. During calibration, the NIRS monitor may consider that the increased attenuation slope is due to a higher absorbing tissue (rather than any problems in the detectors) and will therefore pass the detectors as functioning normally. The bias in the attenuation slope will eventually cause a bias in TOI. To summarize, we found that c-TOI can be biased by the imperfection of the detection probe, although a definite conclusion cannot be drawn.

With a precision of a single measurement of 5.2%, the method lacks preciseness.[3] We tried to reduce this problem by repeated measurements. Our mean c-TOI was 75% (95%CI 72.8 to 76.2%). To put this number in physiological perspec-

tive, we can estimate that a c-TOI of 75% and an arterial saturation S_aO_2 of 95% gives a cerebral venous oxygen saturation (S_vO_2) of 65%, using the formula $(S_aO_2 \times 1/3) + (S_vO_2 \times 2/3) = TOI = 75\%$. Incidentally, this is widely accepted as the normal physiological level of the cerebral venous oxygen saturation. For comparison, Naulaers et al. reported a median c-TOI of 57% (95%CI 54 to 65.7%) in 15 premature infants on the first day of life.[5] This value is abnormally low and may suggest increased cerebral oxygen extraction, and it points to elements of clinical care that may have reduced the cerebral blood flow. Considering the possibilities that c-TOI can be biased by both tissue inhomogeneities and detection probe imperfection, this conclusion can be drawn only with caution.

In conclusion, while c-TOI may be used for trend monitoring satisfactorily, it has previously been shown that c-TOI lacks precision as an absolute measure. Our approach using multiple measurements in each infant to reduce the imprecision exposed an unexplained systematic probe-dependent bias. This deserves further study, as c-TOI is on the verge of entry into routine clinical monitoring. A better strategy to detect potential instrumental problems will be useful in preventing biased c-TOI from occurring.

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References

1. S. Suzuki, S. Takasaki, T. Ozaki, and Y. Kobayashi, "A tissue oxygenation monitor using NIR spatially resolved spectroscopy," *Proc. SPIE* **3597**, 582–592 (1999).
2. G. Greisen and K. Borch, "White matter injury in the preterm neonate: the role of perfusion," *Dev. Neurosci.* **23**, 209–212 (2001).
3. L. C. Sorensen and G. Greisen, "Precision of measurement of cerebral tissue oxygenation index using near-infrared spectroscopy in preterm neonates," *J. Biomed. Opt.* **11**, 054005 (2006).
4. M. S. Patterson, B. Chance, and B. C. Wilson, "Time-resolved reflectance and transmittance for the noninvasive measurement of tissue optical properties," *Appl. Opt.* **37**, 779–791 (1989).
5. G. Naulaers, G. Morren, S. van Huffel, P. Casaer, and H. Devlieger, "Measurement of tissue oxygenation index during the first three days in premature born infants," *Adv. Exp. Med. Biol.* **510**, 379–383 (2003).