Precision of measurement of cerebral tissue oxygenation index using near-infrared spectroscopy in preterm neonates

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Abstract. The use of cerebral tissue oxygenation index (c-TOI) in a clinical setting is limited by doubts concerning the accuracy of the measurements. Since there is no gold standard, validation is difficult. Our modest aim was to quantify the precision of c-TOI doing repeated measurements by reapplying the optode several times presuming no regional differences in cerebral oxygenation. Thirty-seven premature infants were examined with several measurements of c-TOI using the NIRO 300 oximeter. Three to eight measurements were done on each infant over a period of 15 to 25 min. One-way analysis of variance was used to estimate within- and between-infant variation. The median gestational age was 27.6 weeks (23.9 to 33.0). Mean c-TOI (n=253) was 74.6±8.5%. The within-infant variation was 5.2% when resiting the optode. For comparison, the between-infants variation was 6.9%, while the spontaneous 2-sec variation was 2.9%. The precision of a single measurement of c-TOI was not good. By measuring five times instead of one on each subject, the precision of the mean can be assumed to be comparable to pulse oximetry. This may be too cumbersome for clinical use, but may reduce sample size in research.
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Keywords: near-infrared spectroscopy; tissue oxygenation index; premature infant; reproducibility.

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1 Introduction

Spatially resolved spectroscopy (SRS) is a relatively new tool introduced to evaluate brain oxygenation.[1] The light is led to the tissue of interest by an optode, and three closely placed photodiodes detect the returning scattered light. This allows for the determination of the ratio of oxygenated (O_2Hb) to total hemoglobin (Hbc) [O_2Hb+HHb (deoxygenated Hb)] in absolute terms [%]. The name of the ratio is tissue oxygenation index (TOI) and gives a quantitative measure of the hemoglobin oxygen saturation. TOI is related to venous oxygen saturation but is expected to be higher, since blood in capillaries and arteries also contribute to the signal. In patients with normal arterial oxygenation, TOI can be used as a surrogate measure of venous saturation. The cerebro-venous saturation is tightly regulated in healthy individuals and cerebral TOI (c-TOI) should therefore be a sensitive measure of cerebral oxygen sufficiency. Across a range of c-TOI of 40 to 80%, comparisons to venous jugular bulb saturation in infants weighing 4 to 10 kg, showed a mean difference as small as −0.3% but limits of agreement as wide as −11.6 to 11%.[2] This lack of precision limits the use of c-TOI in discriminating normal from abnormal. With a high precision (i.e. reproducibility) method, one measurement would be enough. If the method is less reproducible, repeated measurements using mean values is an alternative. The precision will improve, since standard error of the mean (SEM) is reduced by the square root of the number of measurements.

Cerebral hypoxia due to ischemia could be an explanation why premature born infants have an increased risk of developing brain damage.[3] In this context, the c-TOI could be valuable. Jugular venous bulb saturation cannot be measured in very preterm babies, whereas near-infrared spectroscopy (NIRS) is particularly suitable, because of the thin skull of the infant and the noninvasiveness of the procedure. Regional differences in the cerebral oxygenation may be significant with focal pathology (i.e. middle cerebral artery infarction). Since such lesions are rare in preterm infants, we found it reasonable to assume that the regional differences in c-TOI are negligible under normal circumstances. Our modest aim was therefore to investigate the precision of c-TOI by repeated measurements in a cohort of premature infants.

2 Materials and Methods

Thirty-seven premature infants with a gestational age (GA) below 33 weeks admitted to the Neonatal Care Unit, National

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Table 1 Demographic data.

Case number	37 infants
Sex	16 males/21 females
Gestational age (weeks)	27.6 [23.9 to 33.0]
Birth weight (grams)	1.050 [630 to 2.590]
Saturation (%)	96±2.8
MAPB (mm Hg, n=24)	36±5.9
Inspiratory oxygen concentrations (%)	26±7.7
Respirator treatment [n (%)]	5/37(14%)
n-CPAP [n (%)]	31/37(84%)
No respiratory support [n (%)]	1/37 (2%)

Mean±SD or median [range] when appropriate

University Hospital, Copenhagen, were included. The demographic data of the infants included are summarized in Table 1. Our goal was to examine the infants within the first 24 h after birth. The mean age at examination was 19±6 h. The Danish Ethical Committee [Journal No. (KF) 01-116.04] approved the project and informed parental consent was obtained in all cases.

The tissue oxygenation monitor, the NIRO 300 oximeter from Hamamatsu Phototonics (Hamamatsu Phototonics, Hamamatsu City, Japan) was used. The NIRO 300 is a two-channel oximeter with an emitter optode providing class I laser light with four different wavelengths (775, 810, 847, and 919 nm). By conventional spectroscopy, concentration changes of the tissue chromophores are calculated using the modified Beer-Lambert Law.[4] SRS measures light attenuation as a function of distance from emitter to detector. In NIRO 300, the light is detected by a row of three photosensors. The detector is placed in the probe holder with the row of photosensors in line with the light-emitting optode. Light is attenuated due to scatter and absorption. The diffusion approximation assumes homogenous optical characteristics of the tissue. For SRS, furthermore, the reduced scatter coefficient is assumed to be constant across the range of wavelength.[1] The ratio $(k\times O_2Hb)/(k\times O_2Hb+k\times HHb)=TOI$ [%] is used, where k is the constant reduced scattering coefficient $\mu s'(\lambda)$.[1]

The emitter and the detector were fixed in a nontransparent, soft probe holder specially suited for the purpose (Hamamatsu Phototonics, Hamamatsu City, Japan). The interoptode distance (IOD) was 4 cm. The probe holder was placed in the frontotemporal or frontoparietal region depending on the head size and curvatures. Since the size of the infants varied [birth weight (BW) 630 to 2.590 g] talking of a uniform positioning is an illusion. Instead the most optimal condition for cerebral NIRS was aimed. The curvatures of the head were avoided, so the line between emitter and detector was kept as straight as possible. The detector was placed frontally to avoid hair. The Probe holder was held in position by hand. The signal quality was checked by the initialization procedure before start and after each optode resiting. No measurements were excluded unless the light intensity was inappropriate for the photosensors resulting in an instrumental warning of insufficient signal quality. In this situation, the probe was removed and replaced and c-TOI was measured again. The sensor was held in place until a stable signal tracing was seen on the screen of the instrument and at least for 1 min. The signal was sampled in 2-sec bins. Data were stored on a computer disk for subsequent analysis.

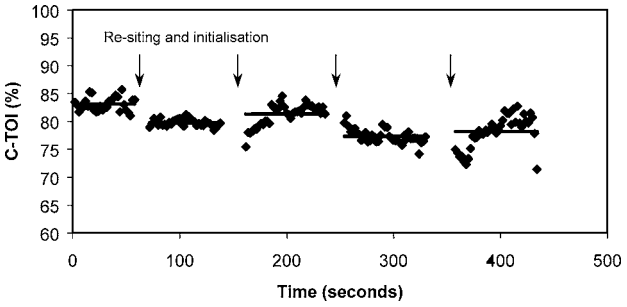

Fig. 1 Estimation of the variability of c-TOI. The figure shows five measurements within one infant. The arrows indicate resiting of the optode, initialization, and a new measurement. Every dot represents a 2-sec TOI value. The 2-sec variation is the variation of TOI within a measurement. The horizontal lines represent the mean TOI for each measurement. The within-infant variation is the variation between the mean TOI values.

The precision of c-TOI was evaluated by resiting the optode in different positions still fulfilling the criteria mentioned above (Fig. 1). The probe was replaced three to eight times depending on the head size and the clinical condition of the infant. The median number of TOI measurements was seven times. Readings on each location was done over a mean of 2.25±1.33 min, but for a minimum of 1 min. One person (L.C.S.) did all measurements.

Simultaneous measurements of mean arterial blood pressure (MABP) were obtained by either a transducer in an indwelling umbilical catheter or by an oscillometric technique using an inflatable cuff. Arterial oxygen saturation (S_aO_2) and pulse rate (PR) were assessed by pulse oximetry.

3 Statistics

Mean c-TOI and standard deviation on each individual location for every infant was determined. C-TOI data was normally distributed. Repeated-measures analysis of variance (ANOVA) using a random effects model with c-TOI as a dependent variable and infant number as a random effect was used to estimate the between- and within-infants variation. Residual plot showed variance homogeneity. The residual standard deviation S_{res} (i.e. the square root of the mean square error) corresponds to the pooled within-infant standard deviation. The between-infants variation was estimated using the formula $\sigma_B^2=(s_B^2-s_W^2)/n_0$ where $n_0=1/(k-1)(\Sigma n_i^2/N)$ correcting for the unequal number of measurements.[5]

The spontaneous 2-sec variation of c-TOI, defined as the variation in c-TOI when measuring at the same point, was calculated using the formula $s^2(n-1)=ss$, where s is the standard deviation; n is the number of measurements upon which the standard deviation is determined; and ss is the sum of

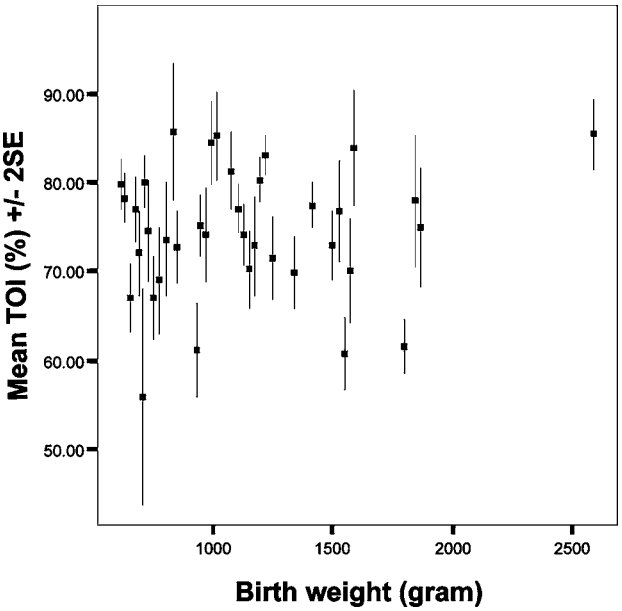

Fig. 2 Mean c-TOI ± 2SE in relation to birth weight. Mean c-TOI for 37 preterm infants. Mean and 95% confidence intervals were calculated from three to eight measurements in each infant. No relation between c-TOI and the size of the infant is apparent.

squares. The total sum of squares was divided by the total number of data entries to obtain the mean spontaneous 2-sec variation $s=(SS/N)^{1/2}$.

To test the relationship between c-TOI and GA and BW, a general linear model was constructed, using c-TOI as the dependent variable and GA and BW as covariates. Data are given as mean±standard deviation (SD). $P<0.05$ was considered statistically significant. All results were analyzed with SPSS 12.0 for WINDOWS.

4 Results

C-TOI was measured 253 times in the 37 infants; values ranged from 50.9 to 96.4%. The grand mean c-TOI ($n=253$ measurements) was 74.6±8..5% (with a 95% confidence interval of 73.9 to 75.3%). The infant with the lowest measured c-TOI had a mean c-TOI of 55.9±4.9%. The infant with the highest measured c-TOI had a mean TOI of 85.7±8.3% (Fig. 2). There was no significant relation between c-TOI and GA ($p=0.115$) or c-TOI and BW ($p=0.189$).

Repeated-measures ANOVA revealed a residual standard deviation S_{res} of 5.2% corresponding to the within-infant variation of c-TOI doing repeated measurements with resiting. The between-infants variation was 6.9% (Table 2). The spontaneous 2-sec variation was 2.9%.

Table 2 One-way ANOVA.

	Type II sum of squares	df	Mean square	Variation
Between infant	12497.524	36	347.153	6.9%
Within infant	5804.879	216	26.874	5.2%
Total	18302.403	253	374.027	8.5%

5 Discussion

In neuro–intensive care a quantitative noninvasive measure of the cerebral oxygenation would be welcome. To determine the reproducibility of TOI, we estimated the precision of c-TOI by replacing the optode several times on each subject.

We resited the optodes over an area as wide as possible, still adhering to the criteria for optimal measurements. This is the strength of our study. When comparing differences among infants, there is no such thing as "the same spot." Although external landmarks may define the placement, it is very unlikely that gyral geometry and cerebro-spinal fluid space are identical from infant to infant. Furthermore it is also unlikely that there are major general regional differences in c-TOI. Regional differences in blood flow[6] and cerebral metabolic rate[7] are an issue. Any regional difference in oxygen requirement (i.e. related to a difference in neuronal activity), however, will induce a parallel difference in local cerebral blood flow by very robust coupling of local blood flow to local oxygen consumption. Hence the effect on c-TOI is expected to be negligible. During functional activation, the situation may be different. Bartocci et al. stimulated premature neonates with an unpleasant odor resulting in a decrease in HbO_2 of about 5 μmol/l and no change in HHb.[8] Assuming a cerebral hemoglobin concentration of 50 μmol/l, unpleasant odors thus would result in a 10% reduction in c-TOI.[8] In contrast, visual stimulation as presented by Meek et al. showed concurrent changes in O_2Hb and HHb and thus would result in only minor changes of the oxygenation index.[9] We measured in a resting situation, although some arousal when replacing the sensor cannot be entirely excluded.

A likely source of variation in c-TOI is related to exact gyral geometry and in particular to cerebro-spinal fluid space geometry. This will result in local differences in scattering and hence violate the assumption of isotropy of scatter and induce measurement error. Therefore, in practice, a measurement in a new infant means a partly new geometry. We have tried to probe this problem with our analysis.

Another source of error is the presence of hair. If there is an inhomogeneous presence of hair below the detectors, this will lead to an erroneous slope ($\delta A/\delta\rho$) and therefore an erroneous TOI. Fortunately, premature infants often have scanty hair, but in an attempt to minimize this source of error, the detector was placed in the least hairy region towards the face.

Our study design has weaknesses too. Intracerebral pathology like focal vasoparalysis, a parenchymal hemorrhage or excess cerebral blood flow (CBF) could theoretically influence the NIRS measurements and increase the within-infants variation. All the infants in our study had normal cerebral ultrasound just before or just after c-NIRS monitoring. Later, three infants (8%) developed major intraventricular hemorrhage (grade IV with involvement of the parenchyma).[10] Neonatal stroke is rare in preterm infants. Arousal by replacing the sensor, however, could account for some of the variation. We decided to keep the probe in position by hand, like others have.[11] A fixing bandage would have been more stressful for the infant because of the several replacements. Differences in

application pressure can induce variability, but a bandage delivering a standardized pressure does not exist.

The within-measurement variation can be seen as partly due to physiological variation in arterial oxygen saturation or in CBF, partly due to error, that is, error of the estimation of absorption as transmitted through the computation of c-TOI and error due to spontaneous movement with the distortion of geometry that follows. But still, the spontaneous variation is rather small. The spontaneous "point-to-point" variation was 2.9%. This means that only 0.35% $[2.9\%/(67)^{1/2}]$ of the 5.2% within-infant variation was due to instability of the c-TOI signal. Since our measurement period is rather short, the spontaneous fluctuations may be underestimated. Yanowitz et al. examined the variability of oxy-, deoxy-, and total hemoglobin in a similar group of infants but for a longer time period (120 min).[12] They found a short-term variability not far from ours and a minute-to-minute variability of similar magnitude.

A previous publication on the reproducibility of c-TOI in neonates with repeated measurements deviates much from our results.[11] This study found a very low within-infant variation (1.7%). Also the between-infant variation after replacement of the optode was lower (4.1%). The reason for this is unclear, but some differences should be discussed. We used NIRO 300; whereas Menke et al. used the Criticon™ Cerebral RedOx Monitor 2020. These two monitors differ in their operating principles. The Critikon 2020 does use four wavelengths, but has only two detectors separated with a distance of 10 mm and 37 mm from the emitter, respectively.[13] A light-emitting diode is placed between the two detectors ensuring that the light intensity at the two detectors is the same. Theoretically the superficial layers mainly affect the signal at detector 1, while the signal at detector 2 also refers to the brain due to the larger IOD and therefore deeper penetration. By calculating a ratio of the signals at detector 2 and detector 1, the influence from the outer layers can be reduced.[13] Wolf et al.[13] examined the function of Critikon 2020 using a liquid neonatal head phantom. With increasing scatter, the deviation from the expected values increased and the concentration changes were underestimated by a factor six to ten.[13] McKeating et al. compared the function of Critikon 2020 with Invos 3100 (Somanetics Corporation, USA)[14] in adult resting volunteers. They failed to obtain stable or readable readings in 44% of the examined subjects.[14] Although their population was a more homogenous group than ours, the SD was remarkable small (2.2%) with a cerebral oxygen saturation (rSO_2) between 64.0 and 71.3%. The Invos 3100, in comparison, found a much larger variation in the same subjects with a rSO_2 range from 56.7 to 75.3% and a SD of 6.1%.[14] In conclusion, we suspect that the Critikon 2020 underestimates true variability of c-TOI.

In research there is an important benefit of repeated measurements. In our study, using only the first measurement from each infant, the c-TOI was 74.7% (SD 9.4%). With a population standard deviation of 9.4% doing only one measurement, a study to detect a clinical relevant difference of 5% in c-TOI with a power $(1-\beta)$ of 0.90 and a significance limit (α) of 0.05 needs a sample size of 75 infants in each group. Doing 5 measurements, the population standard deviation is reduced to 6.9% and only 40 infants is needed in each group.

Precision is important, since c-TOI is a relatively insensitive measure of cerebral oxygen delivery. We found a within-infant variation of 5.2%; hence, the standard error (SE) with 5 measurements was 2.3%. We can estimate how much CBF should differ due to changes a difference in arterial partiel pressure of carbon dioxide ($PaCO_2$) or in MABP to result in a 2.3% difference (1 SE) in c-TOI (for example a decrease from 75% to 72.7%). NIRS is presumed to detect hemoglobin in tissue in a venous-to-arterial ratio of 2:1.[15] This corresponds to $(S_aO_2\times 1/3)+(S_vO_2\times 2/3)=\mathrm{TOI}$. If c-TOI is 75% and S_aO_2 is 95%, then the formula $[(95\times 1/3)+(S_vO_2\times 2/3)=75\%]$ gives a cerebro-venous saturation of 65%. This corresponds to an oxygen extraction (OE) 30%. If TOI were reduced to 72.7%, due to a lower $PaCO_2$ or mean arterial blood pressure, the cerebro-venous saturation can be assumed to be reduced to 61.6%. This corresponds to an oxygen extraction of 33.4%. Hence a decrease in c-TOI by one SE corresponds to a 3.4% decrease in cerebro-venous saturation, and a 10% difference in oxygen extraction. Using the formula $\mathrm{CMR\text{-}O_2}$ (cerebral metabolic rate of oxygen)$=\mathrm{CBF}\times\mathrm{OE}$ this again can be assumed to correspond to a 10% reduction of CBF. This is about the precision of measurement of CBF with 133Xe clearance[16] and better than the precision of measurement of CBF by conventional NIRS.[17] This analysis is relevant for studies comparing c-TOI among infants or within infants after resiting of the optodes. Short-term variation of c-TOI is much less and may or may not be less if the optode is left in place over longer time periods.

It is notable that our mean value on day 1 was 74.6% and the between- infant variation was 6.9%. The population 95% confidence interval based on repeated measurement of c-TOI hence was 60.8 to 88.4%. This is far wider than expected from the narrow range of arterial oxygenation observed and the normal tight physiological control of cerebro-venous saturation. Since none of the infants were severely ill, the wide range probably reflects the cerebro-vascular vulnerability or pathology in this group of very preterm, newly born infants as previously evidenced by a wide range in CBF.[18,19]

For clinical use, a single measurement of c-TOI appears too imprecise and we believe that using 15 to 20 min to resite the optode 5 times is too cumbersome to be practical.

In conclusion, we found the precision of a single measurement of c-TOI to be 5.2% using a commercially available instrument. For clinical use, this is insufficient. In research projects, the sample size can be reduced considerably by the use of repeated measurements of c-TOI.

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