ORIGINAL ARTICLE

Cerebral tissue oxygenation index in very premature infants

G Naulaers, G Morren, S Van Huffel, P Casaer, H Devlieger

Aim: To describe normal values of the cerebral tissue oxygenation index (TOI) in premature infants.

Methods: TOI was measured by spatially resolved spectroscopy in preterm infants on the first 3 days of life. Infants with an abnormal cranial ultrasound were excluded. Other simultaneously measured variables were PaO₂, PaCO₂, pH, mean arterial blood pressure, heart rate, haemoglobin, glycaemia, and peripheral oxygen saturation.

Results: Fifteen patients with a median postmenstrual age of 28 weeks were measured. There was a significant increase in median TOI over the first 3 days of life: 57% on day 1, 66.1% on day 2, and 76.1% on day 3. Multiple regression analysis showed no correlation between TOI and postmenstrual age, peripheral oxygen saturation, mean arterial blood pressure, PaO₂, PaCO₂, and haemoglobin concentration.

Conclusion: Cerebral TOI increases significantly in the first 3 days of life in premature babies. This increase probably reflects the increase in cerebral blood flow at this time.

PATIENTS AND METHODS
Fifteen patients with a postmenstrual age of less than 31 weeks were included. The median postmenstrual age was 28 weeks (range 25–30). A brain ultrasound was performed on all patients before measurements were started. Exclusion criteria were an abnormal brain ultrasound before the TOI measurement and severe pulmonary hypertension as evidenced by echocardiography and/or congenital malformations.

An NIRO 300 (Hamamatsu Phototonics K.K., Tokyo, Japan) was used for spatially resolved spectroscopy. The optode was placed at the right frontoparietal side with the sensors at 4 cm distance. All patients were measured within 6 hours of birth for at least 30 minutes. The second and third measurements were performed 24 and 48 hours later. The specific variable measured was TOI.

Spatially resolved spectroscopy is a new method, using near infrared spectroscopy (NIRS), for measuring cerebral haemoglobin oxygen saturation. The tissue oxygenation index (TOI) is measured with a light detector with three sensors placed at different distances from the near infrared light source. If light with a given intensity is sent into tissue, it is attenuated because of “scatter” loss and “absorption” loss. If the distance between the light source and the sensor is large enough, the isotropy of scatter distribution becomes so homogeneous that the scatter loss is the same at the three sensors. Therefore any differences in intensity measured at the three different sensors can be interpreted as differences in absorption loss. Thus the local absorption change can be seen as a function of the distance between the light source and the three sensors. With this information, an oxygenation index can be calculated using a previously reported algorithm.

Several research groups have measured TOI in healthy adults with different NIRS instruments, and no differences in TOI values between the right and left forehead have been found. To our knowledge, no normal cerebral TOI values in the first days of life have been reported for premature babies (less than 30 weeks gestation). In this study, we measured TOI on days 1, 2, and 3 to obtain “normal” values and to investigate changes with postnatal age.

The simultaneously studied electrocardiogram, pulse rate and peripheral oxygen saturation (beat to beat, on a Nellcor-2000 monitor), and mean arterial blood pressure (Siemens, Sirecus) were recorded in an analogous way with a sampling frequency of 100 Hz by the data acquisition system Codas (Dataq Instruments, Akron, Ohio, USA) and stored in a PC. The NIRO-300 signals are digital and recorded with a sampling rate of 6 Hz. They are converted into analogue signals with a sample and hold function before their introduction into the Codas system. PaO₂, PaCO₂, pH, glycaemia, haemoglobin, and percentage of fetal haemoglobin were measured in an arterial blood sample on a blood gas analyser (Radiometer, Copenhagen, Denmark) before and after the measurement. The same author (GN) performed all the measurements.

Analysis of variance was applied to see if there was a significant difference between TOI and postnatal age. The Student-Newman-Keuls test was used for all pairwise comparisons. p<0.05 was considered significant. Multiple regression analysis was used to detect significant effects of the other variables on TOI.

RESULTS
Fifteen patients were studied during the first 3 days of life. The mean (SD) birth weight was 1053 (395) g, and the mean (SD)
Table 1 Median and 95% confidence interval for tissue oxygenation index, THI, mean arterial blood pressure, peripheral oxygen saturation, \( \text{Paco}_2 \), \( \text{PaCO}_2 \), haemoglobin, and fetal haemoglobin on days 1, 2, and 3.

<table>
<thead>
<tr>
<th>Day</th>
<th>TOI (%)</th>
<th>THI (au)</th>
<th>MABP (mm Hg)</th>
<th>Saturation (%)</th>
<th>( \text{Paco}_2 ) (mm Hg)</th>
<th>( \text{PaCO}_2 ) (mm Hg)</th>
<th>Hb (g/dl)</th>
<th>Fetal Hb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57 [54 to 65.7]</td>
<td>37.8 [15 to 64.1]</td>
<td>32 [30.7 to 39.6]</td>
<td>96.3 [94.5 to 98]</td>
<td>62 [57 to 96]</td>
<td>31 [26 to 38.1]</td>
<td>14.1 [12.3 to 15.5]</td>
<td>86.7 [81.8 to 91.6]</td>
</tr>
<tr>
<td>2</td>
<td>66.1 [61.9 to 82.2]</td>
<td>31.1 [12.3 to 51.2]</td>
<td>36 [34 to 42.1]</td>
<td>96 [92 to 98.5]</td>
<td>55 [49.9 to 72]</td>
<td>45 [37.9 to 49.4]</td>
<td>13 [11.6 to 15.2]</td>
<td>85.5 [72.2 to 90]</td>
</tr>
<tr>
<td>3</td>
<td>76.1 [67.1 to 80.1]</td>
<td>23.7 [14 to 61.6]</td>
<td>41 [37.4 to 45]</td>
<td>95.1 [92.1 to 97.5]</td>
<td>57.5 [53.3 to 65]</td>
<td>36.5 [31 to 43]</td>
<td>14.1 [12.3 to 15.5]</td>
<td>69.7 [56.9 to 82.4]</td>
</tr>
</tbody>
</table>

**p Value:**
- 0.005
- 0.49
- 0.03
- 0.44
- 0.067
- 0.49
- 0.49
- 0.006

*Significant difference (p<0.05) from day 1 (analysis of variance).
**Significant difference (p<0.08) from day 1 (analysis of variance).
*Significant difference (p<0.05) from day 2 (analysis of variance).

**DISCUSSION**

NIRS is a non-invasive method for measuring oxygenated and deoxygenated haemoglobin and derived values of brain oxygenation, cerebral blood flow, and cerebral blood volume. Until now, it has been used only in research because it is very sensitive to movement artefacts. Furthermore, it does not provide absolute values, only values relative to the starting point in a continuous way; TOI, in contrast, is an absolute value and can be measured on different occasions in the same patient. Although in this study TOI was determined in very premature babies and their head circumference was small, very stable TOI values with a mean standard deviation of 2.2% were obtained from measurements taken over at least 30 minutes.

Whether TOI mainly reflects cerebral venous saturation is still under discussion. Several studies report TOI values obtained in healthy adult volunteers. Quaresima et al compared TOI with cerebral venous oxygen saturation, measured by NIRS (NIRO 300, Hamamatsu), and concluded that TOI mainly reflected saturation of the intracranial venous compartment. Two studies using different NIRS instruments also found a correlation, but between TOI and jugular bulb oximetry. Other studies comparing jugular bulb oximetry with TOI did not find any correlation. Al-Rawi et al measured TOI in 60 patients undergoing endarterectomy. They found a significant correlation between TOI and flow velocity, measured by transcranial Doppler of the ipsilateral middle cerebral artery. The change in TOI was predominantly associated with internal carotid artery clamping, and a change during external carotid artery clamping was only seen if there was also a change in blood pressure. The sensitivity of TOI to intracranial and extracranial changes, when there were no blood pressure changes or an extracranial to intracranial anastomosis, was 87.5% and 0% respectively. They conclude that TOI predominantly measures intracranial changes.

Another important finding was that a decrease in TOI is much more

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*Image of box and whisker plot showing the median and interquartile range for the tissue oxygenation index (%) measured on days 1, 2, and 3. The increase from day 1 to day 2 and from day 1 to day 3 was significant (p<0.05).*
important than the absolute value. Different patients had dif-
ferent absolute values, but they all showed a large decrease
when the internal carotid artery was clamped (mean (SD) difference in TOI = −9.4 (7.1%)).

In adults, normal TOI values have been reported to range
from 65% to 85%.15 Teller et al.16 reported TOI values for the liver
and brain during feeding in 25 infants, aged 1–54 days (mean 15.2)
with a postmenstrual age of 29–40 weeks (mean 34 weeks
and 1 day) and a weight of 1400–3365 g (mean 2385). Mean
(SD) TOI of the brain was 62.1 (9.7%), which is lower than the
values reported in adults. They are comparable to our results
on day 1 (59.2 (6.4)%), although TOI values on days 2 and 3 were
higher and more compatible with the results in adult
volunteers.17 Dani et al.18 described mean cerebral oxygen
saturation during caffeine (group A) and aminophylline (group
B) treatment in 40 infants with a mean (SD) gestational age
of 30.4 (3) weeks in group A and 29.4 (1.4) weeks in group B. The
postnatal age was 19 (13) days in group A and 22 (13) days in
group B. The mean cerebral oxygen saturation before and after
treatment ranged from 68.5 (9.1) to 70.1 (6.6)% in group A and
from 64.6 (13.3)% to 68.1 (15)% in group B. These results are
comparable to our results on days 2 and 3.

There are different plausible explanations for the increase in
TOI found in this study during the first 3 days of life. An increase
in oxygenation was ruled out by including only the results
obtained while peripheral oxygen saturation remained
stable. Also arterial oxygen content did not change signifi-
cantly on the different days. Haemoglobin content decreased
day 1 to day 3, but no significant correlation was found
with TOI. Fetal haemoglobin content decreased significantly,
but again no correlation was found with TOI. Further studies
are indicated, as fetal haemoglobin was measured in only
eight patients.

One explanation for the increase in TOI is an increase in cer-
ебral blood flow, as has been found previously.15,17 Meek et al.18
described a significant increase in cerebral blood flow during
the first 72 hours in premature infants, independent of mean
arterial blood pressure, PaCO2, and packed cell volume. An
important bias in our study is the low PaCO2 values on the first
day. This could partly explain the lower cerebral blood flow and
hence the lower TOI values, although we found no correlation
between PaCO2 and TOI. In adults no correlation was found
between TOI and PaCO2.16 A decrease in cerebral blood flow
during hypoxia is well described in neonates. The combination
of low PaCO2, low blood pressure may explain a
lower cerebral blood flow and hence a greater oxygen uptake
with a lower venous saturation. Measurements of the venous
oxygenhaemoglobin saturation confirm this hypothesis. Venous
oxygenhaemoglobin saturation can be measured by NIRS with
partial jugular venous occlusion. Yoxall et al.20 validated this
technique with co-oximetry of jugular bulb blood obtained
during cardiac catheterisation in infants and young children. When
cerebral blood flow and cerebral venous oxygenhaemoglobin
saturation are measured, cerebral oxygen consumption can be
calculated. An increase in cerebral oxygen consumption was
found with advancing gestational age.19 Wirdle et al.20 found an
increase in the fractional oxygen extraction with a decrease in
PaCO2 and an increase during blood transfusion. This may explain
the lower TOI in our patients on the first day when there was a
significantly lower PaCO2.

We found no relation between TOI and neurological
complications or retinopathy, but the measurements were
limited to half an hour a day. The neurological and ophthalmic
complications may be related to hypoxia on the first day. In
preterm babies, a statistical correlation has been found in
different studies between hypoxia and brain damage and
later developmental deficit.21

Yoxall et al.20 suggest that measurement of cerebral oxygena-
tion gives more information than measurement of cerebral
blood flow for the prevention of cerebral hypoxia and ischae-
mia. Measurements of venous oxygenhaemoglobin saturation,
cerebral oxygen consumption, and cerebral fractional oxygen
extraction can be performed with NIRS.22,23 However, measure-
ment of cerebral venous oxyhaemoglobin saturation is still
difficult and cannot be performed continuously. TOI is a non-
invasive parameter for measurement of cerebral oxygenation
and may be useful for continuous monitoring of venous oxy-
haemoglobin saturation. Although several validation studies
have been carried out in adults, further studies in animals
need to be performed to study the relation between TOI,
venous jugular saturation, and cerebral blood flow. In
neonates, further studies are needed to determine the relation
between TOI and venous oxyhaemoglobin saturation as
measured by partial jugular venous occlusion. Further clinical
studies should attempt to elucidate the variation in TOI over
several days. These longer lasting measurements may be able
to detect the relation between periods of low cerebral
oxygenation and neurological complications such as peri-
ventricular leucomalacia. As the measurement of TOI is less
sensitive to movement artefacts, these studies may result in a
new way to detect and prevent severe cerebral ischaemia by
continuous monitoring of cerebral oxygenation.

In conclusion, measurement of TOI in premature infants is
a new non-invasive method for measuring aspects of cerebral
brain oxygenation. An increase in TOI over the first 3 days of
life was found in 15 premature babies. This increase in TOI
may reflect an increase in cerebral blood flow during this time.

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REFERENCES

methods in tissue near infrared spectroscopy. Proc SPIE 1995;2389:486–95
2 Suzuki S, Takesaki S, Ozaki T, et al. A tissue oxygenation monitor using
NIR spatially resolved spectroscopy. Proc SPIE 1999;3597:582–92
3 Quaresima V, Sacco S, Iara R, et al. Noninvasive measurement of
cerebral hemoglobin oxygen saturation using two near infrared
4 Samora S, Dori P, Zelenoek I, et al. Cerebral oxygenation in patients
undergoing carotid endarterectomy under regional anesthesia. Stroke
1996;27:49–55
5 Misra M, Stark J, Djouveny M, et al. Transcranial cerebral oxygenity in
cerebral oxygenity in awake carotid endarterectomy. J Clin Anesth
7 Nielsen HB, Boushel R, Madsen P, et al. Cerebral desaturation during
8 Dobbeney PE, Pilkington SN, Janke E, et al. Cerebral oxygenation
measured by near-infrared spectroscopy: comparison with jugular bulb
9 Sapiro KJ, Gopinath SP, Farhat G, et al. Cerebral oxygenation during
10 Burunk A, van der Hoeven G, Meinders AE. A comparison of
near-infrared spectroscopy and jugular bulb oxygenity in comatose
patients resuscitated from a cardiac arrest. Anaesthesia 1998;53:13–19
oxygenation measured by near-infrared spectroscopy and jugular
venous saturation in patients with severe closed head injury. Anesth
Asthma 1999;91:985–90
12 German TJ, Young AER, Manera AT, et al. Excretaaccumulation of
near infrared light influences the detection of increased cerebral
oxygenation monitored by near infrared spectroscopy. J Neurol
Neurosurg Psychiatry 1995;58:477–8
13 Lewis SB, Myburgh JA, Thornton EL, et al. Cerebral oxygenation
monitoring by near-infrared spectroscopy is not clinically useful in
patients with severe closed head injury: a comparison with jugular venous


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