Abstract

Near infrared spectrophotometry (NIRS) is a noninvasive method for measuring oxygenated and deoxygenated hemoglobin in the neonatal brain. Using oxygen as a tracer, it is possible to calculate cerebral blood flow (CBF) and hemoglobin concentration (cHbc), which corresponds to cerebral blood volume, by inducing small changes in arterial oxygen saturation (SaO2). Variability of tcpO2 is considered to be associated with severe retinopathy of prematurity (ROP). A preliminary analysis without control found a 51% incidence of ROP in infants subjected to NIRS measurements whereas among infants who were not exposed to oxygen changes, only 29% developed ROP (stages 1 to 4, p = 0.008). A controlled study (retrospective cohort study) with matched pairs was performed. Thirty-nine premature newborns who had received NIRS recordings were matched with 39 out of 172 infants who had not received NIRS. Using this controlled study design there was no difference in the incidence and severity of ROP between the two groups. The conclusions are that: (1) Small changes in oxygen saturation of 3 to 10% to measure CBF and cHbc did not increase the incidence or the degree of severity of ROP. (2) A controlled study design is important. Analyses of uncontrolled data would have led to the conclusion that oxygen changes as used with NIRS increase the risk of ROP. © 1996 Society of Photo-Optical Instrumentation Engineers.

Key words near infrared spectroscopy; retinopathy of prematurity; arterial oxygen changes; controlled study design.

1 Introduction

Near infrared spectrophotometry (NIRS) is a noninvasive method for measuring oxygenated (HbO2) and deoxygenated hemoglobin (HHb) in the neonatal brain. Using oxygen as a tracer, it is possible to calculate cerebral blood flow (CBF) and cerebral hemoglobin concentration (cHbc), which corresponds to cerebral blood volume, by inducing small changes in arterial oxygen saturation (SaO2).1,2

The method is considered to be safe concerning the irradiation of skin and brain tissue with laser light. In the NIRS system, an internal safety device measures the light reflected from the skin surface, to avoid exposing the retina by detachment of the sensor.3 However, no controlled study of the possible adverse effects on the retina following acute changes in arterial oxygen saturation during NIRS measurements has been published up to now.

The developing retinal vessels are extremely vulnerable to injury and may be obliterated.4 Retinopathy of prematurity (ROP) is a disease of these vessels and can cause blindness in preterm infants. Following the first controlled trial of ROP (previously called retrolental fibroplasia5), a high concentration of inspired oxygen was considered a cause of the disease. This view was challenged in the past decade by different clinical and experimental observations.6 Today the disease is considered to be the result of several factors that are mainly related to extreme prematurity and to the instability of the cardiorespiratory system of high-risk infants.7 Cunningham et al.8 found in a logistic regression adjusted for significant perinatal factors that variability in transcutaneous pO2 is a significant predictor of severe retinopathy of prematurity. The worldwide consensus6 on the classification of ROP is
based on the location (zones 1 to 3) and severity of vascular changes (stages 1 to 5, Table 1).

In a preliminary study we compared infants who underwent NIRS (N = 39) with infants who had no NIRS (controls, N = 188) for all stages of ROP using the whole population of infants ophthalmoscopically examined in our clinic between 1988 and 1994. The incidence of ROP (all stages) was significantly higher in the NIRS group (P = 0.008). Fifty-one percent of the infants who had NIRS developed ROP, in contrast to only 29% without NIRS. Although the infants in both groups were selected according to similar criteria, three possible confounders were identified: gestational age, birth weight, and the duration of oxygen treatment.

Because these preliminary results might be biased by the differences between the two groups, we planned a controlled study with matched pairs to answer the question of whether repeated increases in oxygen as used with NIRS to determine cbf and cHbc could lead to a higher rate or to an increased severity of ROP in preterm infants.10,11

### Table 1 International classification of ROP.9

<table>
<thead>
<tr>
<th>Stage</th>
<th>Vascular changes</th>
</tr>
</thead>
</table>
| Stage 1 | Demarcation line  
Thin white line that separates the anterior avascular retina from the posterior vascularized retina |
| Stage 2 | Ridge  
The line of stage 1 has developed width, height, and volume, extending out of the plane of the retina |
| Stage 3 | Ridge with fibrovascular proliferation  
Extra-retina fibrovascular proliferation is added to the ridge of stage 2 |
| Stage 4 | Partial retinal detachment  
Exudative skip or traction in nature or caused by retinal break |
| Stage 4A | Extramacular detachment |
| Stage 4B | Detachment involving the macula |
| Stage 5 | Total retinal detachment  
Usually funnel shaped |

**Additional changes in ROP**

- Plus disease  
- Additional abnormal tortuosity and dilation of retinal vessels
- Cicatrical (recessed) ROP  
- Represents a broad spectrum of peripheral and posterior retinal and vascular changes

### 2 Patients and Methods

#### 2.1 NIRS Method

The study was carried out with the Critikon Oxygenation Monitor 205. The method of using NIRS is described in detail elsewhere.12

A possible application of NIRS consists in the quantification of hemodynamic variables.13,14 The measurement of cHbc employs a slow oxygenation change over a period of at least 60 s, which is induced by altering the inspired oxygen fraction of infants, who need additional oxygen. During this change the arterial oxygen saturation (SaO₂ in percent) is measured by pulse oximetry together with the concentration changes of cerebral oxyhemoglobin (O₂Hb in μmol/liter), deoxyhemoglobin (HHb in μmol/liter), and total hemoglobin (tHb in μmol/liter) by NIRS. A valid measurement requires a change in SaO₂ of at least 4%. During that time the SaO₂ has to be kept in a normal range between 85 and 95%.

The slope between O₂Hb and SaO₂ is determined by a linear regression. The slope gives the amount of additional O₂Hb per percent change in SaO₂. The absolute cHbc corresponds to the amount of O₂Hb for an extrapolated 100% change in SaO₂:

\[ cHbc = 100 \times \frac{dO_2Hb}{dSaO_2} \left( \frac{\mu mol}{1} \right). \]  

(1)

The Fick principle is used to measure the cbf, taking O₂Hb as tracer. It states that the rate of accumulation (Q) of a tracer (t) in an organ is equal to the difference between its arterial (Ca) and venous (Cv) concentration multiplied by the blood flow (F):  

\[ \frac{dQ}{dt} = F \times (C_a - C_v). \]  

(2)

The left side of Eq. (2) (dQ) can be measured by NIRS. Cₐ is determined by a pulse oximeter (SaO₂) in combination with the arterial hemoglobin concentration (cHb in mmol/liter). If there is a change in Cₐ (e.g., by giving a bolus of oxygen after a steady state), it will take several seconds—the so-called transit time—until it reaches the venous compartment and Cᵥ is affected. If the calculations of flow are based on the data obtained before the transit time has elapsed (e.g., the first 8 s), Cᵥ remains constant and can be neglected, because dQ/dt will only be affected by the change in Cₐ:

\[ cbf = \frac{Q}{\int Ca \times dt} = \frac{\Delta O_2Hb}{cHb \times \int \Delta SaO_2 \times dt} \]

\[ = \frac{5.71 [O_2Hb(t_1) - O_2Hb(t_0)]}{cHb \times \int_0^1 \Delta SaO_2 \times dt} \left( \frac{ml}{100 g \times min} \right). \]  

(3)
The scaling factor of 5.71 evolves from the conversion of 1 l to 100 g brain (density 1.05 g/ml) and time from seconds to minutes (df is in seconds).

For a valid cerebral blood flow measurement, an increase in SaO2 of at least 3% during a period of 8 s is necessary. The bolus of oxygen is given by abruptly raising the fraction of inspired oxygen to 100% for 10 s. Although the SaO2 is lowered to about 90% before the bolus is given, the SaO2 usually rises above 95% for a short period of time.

SaO2 (Pulsoximeter Nellcor 200), transcutaneous paO2 and paCO2 (Hellige Oxi- and Kapnomonitor), heart rate, and mean arterial blood pressure (Hellige Servomed) were simultaneously recorded with the NIRS signals (sample time 10 s) and stored in a computer. Mean arterial pressure was measured with an umbilical arterial line.

### 2.2 EXAMINATION OF ROP

In accordance with the recommendations of the American Academy of Pediatrics and the CRYO-ROP study, ophthalmoscopic monitoring of preterm infants with birth weights below 1,500 g in our unit occurs between the fifth and sixth week of extrauterine life and is continued every 2 weeks until the retina is fully vascularized. The examinations were performed by the same experienced pediatric ophthalmologist (X.M.).

The International Classification of Retinopathy of Prematurity was applied and the most advanced stage of ROP was used for the diagnosis (Table 1).

### 2.3 MATCHING

Thirty-nine infants who had received NIRS were matched with 39 infants who had not received NIRS out of 172 premature infants born between 1988 and 1994 and hospitalized at the Newborn Intensive Care Unit of the University Hospital Zurich. The diagnosis of ROP was masked during the matching process.

The infants were matched by a computer program for gestational age and the smallest difference in duration of oxygen exposure in days. The difference in gestational age was set to be within a range of 7 days (Table 2). The median difference of the two groups was 1 day.

In addition to birth weight, the need for oxygen at 24 and 72 h and evidence of sepsis was compared in the two groups (Table 2). All the infants received vitamin E (12.5 mg Ephynal subcutaneously).

### 2.4 STATISTICS

Statistical analysis was done using chi square or the Man-Whitney-U test, as appropriate. Confidence limits around the treatment effect were calculated according to Detsky and Sacket. The study was approved by the ethical committee of our institution.

### Table 2 Patient data of the matched pairs.

<table>
<thead>
<tr>
<th>Variablesa</th>
<th>NIRSb (n=39)</th>
<th>Controlsb (n=39)</th>
<th>Pc</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA [weeks]</td>
<td>28 (26–31 5/7)</td>
<td>28 1/7 (25–32 4/7)</td>
<td>0.61</td>
</tr>
<tr>
<td>BW [grams]</td>
<td>970 (660–1420)</td>
<td>1040 (690–1440)</td>
<td>0.44</td>
</tr>
<tr>
<td>O2 exposure [days]</td>
<td>52 (0–134)</td>
<td>50 (0–117)</td>
<td>0.49</td>
</tr>
<tr>
<td>FiO2/24 h</td>
<td>0.35 (0–0.82)</td>
<td>0.30 (0–0.84)</td>
<td>0.45</td>
</tr>
<tr>
<td>FiO2/72 h</td>
<td>0.27 (0–0.50)</td>
<td>0.25 (0–0.89)</td>
<td>0.38</td>
</tr>
<tr>
<td>Ventilatory support (days)</td>
<td>11 (0–64)</td>
<td>7 (0–33)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of blood transfusions</td>
<td>1 (0–8)</td>
<td>1 (0–8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Incidence of sepsis</td>
<td>17/39</td>
<td>14/39</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex</td>
<td>24 females</td>
<td>20 females</td>
<td>0.36</td>
</tr>
</tbody>
</table>

a GA, gestational age; BW, birth weight; FiO2/24 h or 72 h, fraction of inspired oxygen at 24 and 72 h of life.
b Values are median [range] or proportion.
c p, Man-Whitney-U test or chi square test.

### 3 RESULTS

The matching procedure resulted in two comparable groups not only in respect to the two matching criteria of gestational age and duration of oxygen exposure, but also in respect to birth weight, FiO2 at 24 and 72 h, incidence of sepsis, and sex. The infants of the NIRS group needed significantly longer ventilatory support compared with the controls. The difference could have affected the prevalence of ROP but obviously did not.

The prevalence of ROP was identical in both groups (20/39). The prevalence of severe ROP (stages 3 and 4) was 3/39 (7.7%) in the NIRS group and 4/39 (10.3%) in the control group, which is not significantly different (Table 3). No correlation was found between the number of oxygen changes and the severity of ROP.

### 4 DISCUSSION

In contrast to the preliminary analysis with unmatched groups differing in size and many variables, the analysis with matched pairs gave the same incidence and severity for ROP in infants investigated for cbf and CHbc with repeated increases in SaO2 and NIRS as for the controls. Thus the null hypothesis can be accepted.
As with every trial with a negative result, the question must be raised: What difference can be excluded with the number of subjects involved? According to Detsky and Sacket,16 it can be ruled out with 95% probability that the incidence of ROP in the NIRS group will exceed that of the control group by more than 22%. It is very unlikely that induced changes in oxygenation decrease the incidence of ROP.

This study underlines the importance of a controlled study design. Uncontrolled data analysis led to the wrong conclusion that oxygen changes as used with NIRS increase the risk of ROP by a factor of two. The controlled study design gives an identical incidence for ROP in both groups and allows us to exclude a difference of more than 22%.

The range of SaO2 was carefully maintained within normal values during induced changes. Therefore we cannot exclude an effect of hyperoxia (SaO2>95%) or hypoxia (SaO2>85%) on the prevalence or severity of ROP.

Due to the test-retest variability of the cbf and cHbc measurement of about 18%, several repeated measurements of these two variables are necessary to reduce variability. Nevertheless we try to limit the number of SaO2 changes to a minimum. Until results of further studies with a larger number of patients are available, caution with the administration of oxygen is still recommended.

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Table 3 Incidence of ROP in the NIRS and control group.

<table>
<thead>
<tr>
<th>Stage of ROP</th>
<th>NIRS [n=39]</th>
<th>Controls [n=39]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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