Cerebral Oxygenation in Preterm Infants With Germinal Matrix–Intraventricular Hemorrhages

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Background and Purpose—Preterm infants are at risk of developing germinal matrix hemorrhages–intraventricular hemorrhages (GMH-IVH). Disturbances in cerebral perfusion are associated with GMH-IVH. Regional cerebral tissue oxygen saturation ($r_{cSO_2}$), measured with near-infrared spectroscopy, and fractional tissue oxygen extraction (FTOE) were calculated to obtain an indication of cerebral perfusion. Our objective was to determine whether $r_{cSO_2}$ and FTOE were associated with GMH-IVH in preterm infants.

Methods—This case–control study included 17 preterm infants with Grade I to III GMH-IVH or periventricular hemorrhagic infarction (median gestational age, 29.4 weeks; range, 25.4 to 31.9 weeks; birth weight, 1260 g; range, 850 to 1840 g). Seventeen preterm infants without GMH-IVH, matched for gestational age and birth weight, served as control subjects (gestational age, 29.9 weeks; range, 26.0 to 31.6 weeks; birth weight, 1310 g; range, 730 to 1975 g). $r_{cSO_2}$ and transcutaneous arterial oxygen saturation were measured during 2 hours on Days 1 to 5, 8, and 15 after birth. FTOE was calculated as FTOE = (transcutaneous arterial oxygen saturation–$r_{cSO_2}$/transcutaneous arterial oxygen saturation).

Results—Multilevel analyses showed that $r_{cSO_2}$ was lower and FTOE higher in infants with GMH-IVH on Days 1, 2, 3, 4, 5, 8, and 15. The largest difference occurred on Day 5 with $r_{cSO_2}$ median 64% in infants with GMH-IVH versus 77% in control subjects and FTOE median 0.30 versus 0.17. $r_{cSO_2}$ and FTOE were not affected by the grade of GMH-IVH.

Conclusions—Preterm infants with GMH-IVH had lower $r_{cSO_2}$ and higher FTOE during the first 2 weeks after birth irrespective of the grade of GMH-IVH. This suggests that cerebral perfusion is decreased persistently for 2 weeks in infants with GMH-IVH, even in the presence of mild hemorrhages. (Stroke. 2010;41:2901-2907.)

Key Words: cerebral oxygenation; fractional tissue oxygen extraction; germinal matrix hemorrhages–intraventricular hemorrhages; preterm infants; near-infrared spectroscopy

Preterm infants are at risk of developing germinal matrix hemorrhages–intraventricular hemorrhages (GMH-IVH). The primary lesion is a bleeding from small vessels in the germinal matrix. The hemorrhage may be limited to the germinal matrix region (Grade I) or it may rupture and extend into the adjacent ventricular system (Grade II or III, depending on the extent of blood in the lateral ventricle). A complication of GMH-IVH is a periventricular hemorrhagic infarction (PVHI), formerly described as Grade IV GMH-IVH. The pathogenesis of GMH-IVH is multifactorial. Some studies hinted at high cerebral blood flow (CBF) being associated with GMH-IVH, whereas others reported that low CBF is associated with increased risk of GMH-IVH. The latter studies, which use different methods to measure cerebral perfusion, seem to indicate that the occurrence of GMH-IVH is preceded by a period of low CBF. An indirect way of measuring CBF is to measure cerebral tissue oxygenation because one function of blood flow is to supply oxygen to tissue. A study in newborn lambs found that cerebral tissue oxygen saturation correlates well with changes in CBF. A noninvasive method used to assess cerebral oxygenation is near-infrared spectroscopy (NIRS). It measures regional cerebral tissue oxygen saturation ($r_{cSO_2}$). This measure reflects the oxygen saturation in a mixed vascular bed dominated by venules. Fractional tissue oxygen extraction (FTOE) is calculated on the basis of $r_{cSO_2}$ and transcutaneous arterial oxygen saturation ($tcSaO_2$) values. $R_{cSO_2}$ serves as an indicator of cerebral hypoxic hypoxia. FTOE reflects the balance between cerebral oxygen supply (cerebral perfusion) and cerebral oxygen consumption and thus serves as an indicator of cerebral ischemic hypoxia.

Our objective was to determine whether $r_{cSO_2}$ and FTOE were associated with GMH-IVH in preterm infants. The majority of hemorrhages evolve within the first 72 hours of postnatal life. We hypothesized that as a result of low
cerebral perfusion, $r_SO_2$ will be lower and FTOE will be higher in infants with GMH-IVH during the first days after birth. We were particularly interested in FTOE, but we also examined $r_SO_2$ because oxygen saturation is what we actually measured.

Patients and Methods

Patient Population

We performed a longitudinal case–control study. We included 17 preterm infants with Grade I to III GMH-IVH, or PVHI. Seventeen preterm infants without GMH-IVH, matched for gestational age and birth weight, served as control subjects. Both sets of infants were selected for post hoc use from a larger cohort of 81 infants in which we measured $r_SO_2$ and FTOE during the first days after birth. The selection criterion was a gestational age of <32 weeks. Infants with major chromosomal or congenital abnormalities were not included in the study. Infants who developed cystic periventricular leukomalacia were not included either because this condition may interfere with cerebral oxygenation in a different way compared with GMH-IVH.19

The infants had all been admitted to the neonatal intensive care unit of the University Medical Center Groningen between May 2006 and February 2008. The study was approved by the Institutional Review Board of the University Medical Center Groningen. Written, informed parental consent was obtained in all cases.

Cranial Ultrasonography

Cranial ultrasound scans were made of all the infants within 72 hours after birth and subsequently at weekly intervals. In case of intracranial hemorrhages, 2 to 3 cranial ultrasound scans were made during the first week. The scans were made through the anterior fontanelle by means of a real-time mechanical sector scanner equipped with a 7.5-MHz transducer. All scans were assessed by 2 experts (A.F.B., A.M.), who were unaware of the NIRS data. They determined the presence of GMH-IVH or PVHI as well as the grade and localization (left/right) of the GHM-IVH or PVHI.1,2 In addition, they noted the presence of posthemorrhagic ventricular dilatation, defined as a lateral ventricle size of >0.33 according to Evans index (the right and left lateral horn width divided by the maximum internal skull width).21

Near-Infrared Spectroscopy

We used an INVOS 4100 monitor (Somanetics Corporation, Troy, Mich) in combination with a pediatric SomaSensor to measure $r_SO_2$ values. The optical sensor measures the quantity of reflected light photons as a function of 2 wavelengths (730 and 805 nm) and determines the spectral absorption of the underlying tissue.14,22 Because oxygenated hemoglobin and deoxygenated hemoglobin have distinct absorption spectra, NIRS can differentiate between the two. The ratio of oxygenated hemoglobin to total hemoglobin reflects the regional oxygen saturation of cerebral tissue.

$r_SO_2$ was measured within the first 24 hours after birth and subsequently on the second, third, fourth, fifth, eighth, and 15th days over a 2-hour period. The measurement was allowed some time to stabilize and therefore the first 15 minutes were not analyzed. The optical sensor was placed on the left frontoparietal side of the infant’s head and held in place with elastic bandaging. We marked the location of the sensor to ensure that the sensor was placed at the same position for each measurement.

Simultaneously, we measured tcSaO$_2$ by means of pulse oximetry. We calculated FTOE as FTOE = (tcSaO$_2$ - $r_SO_2$)/tcSaO$_2$.14–17 FTOE reflects the balance between cerebral oxygen supply and cerebral oxygen consumption.16–18 FTOE serves better as a marker for ischemic hypoxia than $r_SO_2$ alone because it is more independent of changes in arterial oxygen saturation.19

Clinical Variables

Prospectively, we collected details on perinatal and neonatal characteristics that might influence hemodynamics. These included gestational age, birth weight, Apgar score, umbilical cord pH, birth asphyxia, early-onset and late-onset sepsis, signs of circulatory failure, ventilatory status, including mean airway pressure, patency of the ductus arteriosus, and medication. Maternal and pregnancy-related variables included medication, intoxications, intrauterine growth restriction, premature rupture of membranes (>24 hours), pre-eclampsia, and signs of maternal intrauterine infection. The placenta was examined for histological characteristics of inflammation.

The infant’s heart rate, respiratory rate, mean arterial blood pressure, blood gas values, blood glucose, and hemoglobin concentration were recorded simultaneously with the $r_SO_2$ and tcSaO$_2$ measurements.

Statistical Analysis

We used SPSS 16.0 software for Windows (SPSS Inc, Chicago, Ill) for the statistical analyses. The mean and median values for the 2-hour recording periods. For the cross-sectional analyses between groups, median values were analyzed by the Mann–Whitney test for nonnormal distributions. The Spearman rank order correlation test (2-tailed) was used to determine correlations between the clinical and NIRS parameters during the first 2 weeks after birth. Where appropriate, we tested proportions of categorical data with Fisher exact test or the $\chi^2$-for-trend test.

We categorized the infants into 3 groups: no hemorrhages (controls), mild hemorrhages (Grade I to II), or severe hemorrhages (Grade III, PVHI). To determine the relation between the categories of grading of the hemorrhages and the NIRS parameters, we built a multilevel model18 into the statistical program MLwiN 2.15 (University of Bristol, Bristol, UK). This multilevel analysis allowed more accurate statistical testing than the standard repeated measures analysis of variance approach because it allows unequal numbers of observations per individual and it does not assume equality of group variances.24 First, we constructed models in which NIRS measurements (Level 1) were nested within subjects (Level 2) thereby taking into account dependency between measurements and in which the intercept was measured on Day 1 in the group without hemorrhages. The terms were a combination of the levels of the factors day of measurement and hemorrhage category. This led to 7×3=21 terms. Second, to arrive at a model that was both simpler and easier to interpret, each model was simplified by removing one by one those terms that were not included in a higher-order interaction term. This was done on the basis of the criterion that the coefficient of a term did not reach statistical significance ($P>0.05$; backward model selection). We used these simplified models to test differences between weighted means. We used a $t$ test to test for differences between 1 estimated mean and the intercept.21 To test for differences between 2 estimated means, we tested the contrast of the sum of the parameters from which each estimate is derived using a $\chi^2$ test with 1 degree of freedom.

Data were summarized as mean values±SD, as median values and ranges, or as weighted mean difference and a 95% CI where appropriate. A probability value of $<0.05$ was considered statistically significant.

Results

Of the 17 infants with GMH-IVH, 10 had Grade I GMH-IVH, 3 had Grade II GMH-IVH, 2 had Grade III GMH-IVH, and 2 infants had PVHI (Table 1). PVHI was secondary to GMH-IVH in both infants (Grade I and I Grade III). GMH-IVH or PVHI was seen in all infants on the first cranial ultrasound scans that were made within 72 hours after birth. In 1 infant, progression of Grade I to Grade II GMH-IVH was seen on cranial ultrasound scans between the third and the fifth days. No progression of the grade of GMH-IVH was seen in any other hemorrhages of the other infants on subsequent cranial ultrasound scans. Four infants had developed posthemor-
rhagic ventricular dilatation on subsequent cranial ultrasound scans: 1 had Grade I GMH-IVH, 1 Grade II GMH-IVH, and 2 infants had Grade III GMH-IVH. One of the infants with Grade III GMH-IVH received several therapeutic lumbar taps allowing 10 to 15 mL/kg liquor drainage each time.

The perinatal characteristics of the infants with GMH-IVH or PVHI and the control subjects (Table 2) were similar. Two infants died before the 15th day after birth; 1 infant with Grade III GMH-IVH died of multiorgan failure on the eighth day and 1 infant in the control group died of massive lung bleeding on the tenth day after birth.

The Effect of GMH-IVH or PVHI on r$_{c}$SO$_{2}$, FTOE, and tcSaO$_{2}$

Cross-sectionally, we found lower r$_{c}$SO$_{2}$ in preterm infants with GMH-IVH or PVHI on Days 1, 2, 3, 4, 5, and 8 (Mann–Whitney U test, $P<0.05$), but not on Day 15 (Figure 1A). The largest difference appeared on Day 5 with r$_{c}$SO$_{2}$ of 64% (median) in infants with GMH-IVH or PVHI versus 77% in control subjects (Mann–Whitney U test, $P=0.001$). FTOE was higher in preterm infants with a GMH-IVH or PVHI on Days 1, 2, 3, 4, 5, and 8 ($P<0.05$), but not on Day 15 (Figure 1B). The largest difference also appeared on Day 5 with FTOE of 0.30 (median) in infants with GMH-IVH or PVHI versus 0.17 in control subjects ($P=0.001$; Figure 2). TcSaO$_{2}$ did not differ between the 2 groups (Figure 1C). After excluding the infants that had died, we found the same results; that is, significant differences between the 2 groups are marked in the top of the figure by asterisks (*$P<0.05$, **$P<0.005$, ***$P<0.001$, GMH-IVH or PVHI versus control subjects).

Table 1. Distribution of GMH-IVH or PVHI

<table>
<thead>
<tr>
<th>Grade</th>
<th>No.</th>
<th>Left</th>
<th>Right</th>
<th>Left + Right</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>1</td>
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<tr>
<td>II</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>PVHI</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as numbers.

Table 2. Perinatal Characteristics

<table>
<thead>
<tr>
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<th>GMH-IVH or PVHI</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>29.4 (25.4–31.9)</td>
<td>29.9 (26.0–31.6)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1260 (850–1840)</td>
<td>1310 (730–1975)</td>
</tr>
<tr>
<td>Female/male</td>
<td>9/8</td>
<td>9/8</td>
</tr>
<tr>
<td>Apgar score at 5 minutes</td>
<td>8 (5–9)</td>
<td>7 (3–9)</td>
</tr>
<tr>
<td>Umbilical cord pH</td>
<td>7.31 (7.05–7.44)</td>
<td>7.31 (7.17–7.41)</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>27.0 (23.0–29.5)</td>
<td>27.5 (23.0–30.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Circulatory failure</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Fluid resuscitation</td>
<td>9 (53)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Inotropes</td>
<td>3 (17)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Small-for-gestational age (%)</td>
<td>1 (6)</td>
<td>0 (--)</td>
</tr>
<tr>
<td>Maternal preeclampsia (%)</td>
<td>2 (12)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Intrauterine infection (%)</td>
<td>5 (29)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Premature rupture of membranes (%)</td>
<td>6 (35)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Early-onset sepsis (%)</td>
<td>0 (--)</td>
<td>2 (12)</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or as numbers unless otherwise specified. There were no significant differences between groups. Circulatory failure was defined as hemodynamic instability and scored by the need for volume administration or the use of inotropes or both during the first 24 hours after birth. Maternal intrauterine infection was based on clinical signs such as fetal tachycardia and maternal fever ($>38°C$), often combined with the mother taking antibiotics. Early-onset sepsis was diagnosed by a positive blood culture or clinical signs or both within the first 48 hours after birth.

Figure 1. The course of r$_{c}$SO$_{2}$ (A), FTOE (B), and tcSaO$_{2}$ (C) in preterm infants with GMH-IVH or PVHI versus a preterm control group. Data are shown in box and whisker plots. Dots and stars represent outliers. Significant differences between the 2 groups are marked in the top of the figure by asterisks (*$P<0.05$, **$P<0.005$, ***$P<0.001$, GMH-IVH or PVHI versus control subjects).
The Relationship Between the Grade of GMH-IVH or PVHI and \( r_s \text{SO}_2 \) and FTOE

In comparison to the control subjects, we found significantly lower \( r_s \text{SO}_2 \) on all days in infants with mild hemorrhages. This was established by multilevel analyses taking into account the longitudinal study design, the individual infant, and the differences between the days of measurement. The differences were largest on Day 5 (weighted mean difference, 12%; 95% CI, −18 to −6; \( P < 0.001 \)). \( r_s \text{SO}_2 \) was also significantly lower in infants with severe hemorrhages (weighted mean difference, −6%; 95% CI, −9 to −3; \( P = 0.03 \); Table 3). Compared with control subjects, we found a significantly higher FTOE on all days in infants with mild hemorrhages, the differences being largest on Day 5 (weighted mean difference, 0.14; 95% CI, 0.08 to 0.20; \( P < 0.001 \)). FTOE was also significantly higher in infants with severe hemorrhages (weighted mean difference, 0.07; 95% CI, 0.05 to 0.10; \( P = 0.05 \)). We did not find a statistically significant difference in \( r_s \text{SO}_2 \) or FTOE between mild hemorrhage and severe hemorrhage on Days 1, 2, 3, 4, 8, and 15. On Day 5, there was a trend toward lower \( r_s \text{SO}_2 \) (\( P = 0.1 \)) and higher FTOE (\( P = 0.08 \)) in the infants with mild hemorrhages compared with the infants with severe hemorrhages.

The Relationship Between the Localization of the GMH-IVH or PVHI and \( r_s \text{SO}_2 \) and FTOE

We found no difference in left or right localization in any GMH-IVH or PVHI and \( r_s \text{SO}_2 \) or FTOE. Additionally, we found no difference in left or right localization in each grade of GMH-IVH or PVHI and \( r_s \text{SO}_2 \) or FTOE.

The Relationship Between \( r_s \text{SO}_2 \) and FTOE and Perinatal and Neonatal Characteristics in Both Groups

To investigate whether other variables during the perinatal and neonatal period had confounded our findings on cerebral hemodynamics, we checked maternal medication and other intoxications, pre-eclampsia, premature rupture of membranes, signs of placental inflammation, and birth asphyxia. We found no differences between the groups nor did we find differences between the groups with regard to the presence of a patent ductus arteriosus based on clinical signs and confirmed by echocardiography. In addition, we checked mean arterial blood pressure, \( \text{Paco}_2 \), blood glucose, hemoglobin concentration, heart rate, respiratory rate, and ventilatory status during the 2-hour period of measurement (Table 4). Mean arterial blood pressure, \( \text{Paco}_2 \), hemoglobin concentration, heart rate, and respiratory rate did not correlate with \( r_s \text{SO}_2 \) and FTOE. On Day 1, more infants with GMH-IVH or PVHI received ventilatory support through continuous positive airway pressure than control subjects (7 [50%] versus 2 [12%]; \( P = 0.044 \)). No other relationships were found between the 2 groups and type of ventilatory support. Mean airway pressure was not different between the 2 groups either. Furthermore, we checked whether there was a relationship between mean airway pressure and cerebral oxygenation. We found this not to be the case except on Day 4 when we found a negative correlation between mean airway pressure and FTOE (Spearman rho = −0.578, \( P = 0.049 \)). Blood glucose was higher on Day 4 in infants that developed GMH-IVH or PVHI (\( P = 0.007 \)).

Discussion

Our study demonstrated that preterm infants with GMH-IVH or PVHI had lower \( r_s \text{SO}_2 \) and higher FTOE during the first 2 weeks after birth in comparison to infants without GMH-IVH. Lower \( r_s \text{SO}_2 \) and higher FTOE occurred irrespective of the grade of GMH-IVH. These findings were not in line with our hypothesis. We expected \( r_s \text{SO}_2 \) to be lower and FTOE to be higher only during the first days after birth in infants with GMH-IVH or PVHI due possibly to lower cerebral perfusion. Instead, we found differences in cerebral oxygenation lasting at least for the first 2 weeks after birth.

Because FTOE reflects the balance between cerebral oxygen supply and cerebral oxygen consumption, increased FTOE can be explained either by a lower supply of oxygen or by increased oxygen consumption.\(^{16–18}\) A lower supply of oxygen could be the result of a lower CBF. A previous study...
found that CBF measured during the first 24 hours after birth was lower in 7 infants who developed a GMH-IVH compared with 17 infants without GMH-IVH.7 The infants with severe GMH-IVH in particular had the lowest CBF.7 Pryds et al found that 10 infants, who subsequently developed GMH-IVH Grade III or PVHI, had a 20% lower CBF compared with 38 infants with normal cranial ultrasound scans.6 In a larger cohort of 254 preterm infants, a low CBF on the first day after birth was the dominant independent risk factor for the emerging GMH-IVH.9 In these studies, CBF was measured in different ways using131Xenon clearance,6 NIRS,7 sure during the first days after birth. Contrary to the findings of Pryds et al, who subsequently developed GMH-IVH Grade III or PVHI, we found a 10% lower CBF compared with 17 infants without GMH-IVH or PVHI from Days 1 to 15. This suggests that CBF is persistently lower in infants with GMH-IVH or PVHI as compared with control infants, even in the presence of mild hemorrhages. One explanation could be that those infants who have low CBF, but still within the normal range, are at increased risk of acquiring GMH-IVH. Another explanation could be that circumstances leading to a lower CBF, which poses the infant at risk for GMH-IVH, remain present for a longer period than just the first few hours. Finally, the lower CBF could also be secondary to the presence of the hemorrhage itself as was suggested by Ment et al.8

Our study did not reveal whether lower rSO2 and higher FTOE in infants with GMH-IVH or PVHI as compared with infants without GMH-IVH or PVHI from Days 1 to 15. This suggests that CBF is persistently lower in infants with GMH-IVH, even in the presence of mild hemorrhages. One explanation could be that those infants who have low CBF, but still within the normal range, are at increased risk of acquiring GMH-IVH. Another explanation could be that circumstances leading to a lower CBF, which poses the infant at risk for GMH-IVH, remain present for a longer period than just the first few hours. Finally, the lower CBF could also be secondary to the presence of the hemorrhage itself as was suggested by Ment et al.8

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Table 4. Neonatal Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Days 1–5 GMH-IVH Versus Control Subjects</th>
<th>Day 8 GMH-IVH Versus Control Subjects</th>
<th>Day 15 GMH-IVH Versus Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin concentration, mmol/L</td>
<td>8.7†</td>
<td>7.9†</td>
<td>8.7</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>4.5†</td>
<td>4.6†</td>
<td>5.4</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>34†</td>
<td>37†</td>
<td>40</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>2.8†</td>
<td>3.5†</td>
<td>5.7</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>150‡</td>
<td>149‡</td>
<td>155</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory rate, breaths per minute</td>
<td>49‡</td>
<td>47‡</td>
<td>49</td>
</tr>
</tbody>
</table>

Ventilatory support

- Mechanical ventilation: 8§, 14§, 4, 4, 5, 3
- CPAP: 7§, 28*, 7, 3, 2, 3
- Low flow: 0§, 1§, 5, 5, 3, 3

Data are expressed as median or as numbers unless otherwise specified. Differences between groups are marked by asterisks (*P<0.05 GMH-IVH or PVHI versus control subjects).

†Median lowest value over Days 1 through 5.
‡Median value over Days 1 through 5.
§No. on Day 1. Patency of the ductus arteriosus was routinely determined by echocardiography on the third to fifth days after birth if the infants were artificially ventilated, needed continuous positive airway pressure (CPAP), or had other clinical signs suggesting a patent ductus arteriosus.

Although information on the exact timing of the hemorrhages was unavailable, all the infants in our study already showed GMH-IVH or PVHI on the first cranial ultrasound scans that had been made within the first 72 hours after birth. We checked whether progression of GMH-IVH was visible
on cranial ultrasound scans made after the first scan. This was not the case. The largest difference in $r_3SO_2$ and FTOE on the fifth day after birth could, therefore, not be attributed to a progression of GMH-IVH. The strength of our study lies in the fact that we followed these infants during the first 2 weeks after birth. Using multilevel analyses that allowed more accurate statistical testing, we found lower $r_3SO_2$ and higher FTOE from the first day onward until the 15th day. No confounders were identified that could otherwise explain this finding.

A lower supply of oxygen could also be the result of a lower concentration of hemoglobin as a result of the hemorrhage or lower arterial oxygen content. Hemoglobin levels, however, were the same in both groups, ruling out the possibility of a lower oxygen supply related to differences in hemoglobin levels. Furthermore, lower arterial oxygen content was not likely because tcSaO$_2$ did not differ between groups. We also found no differences between the 2 groups with regard to other clinical variables. Thus, we believe that these variables did not account for the differences in $r_3SO_2$ and FTOE between the 2 groups.

A final explanation for higher FTOE is increased oxygen consumption, but this is not very likely. Recently, increased oxygen consumption was found in late preterm and term infants with a large variety of brain injuries. $^{20}$ Possibly, these findings extend to our findings in very preterm infants, although this is purely speculative.

The values we found for $r_3SO_2$ and FTOE showed a wide range. This finding is confirmed by various other studies,$^{14,15,20}$ and points to large interindividual variation. Sorensen et al found a mean $r_3SO_2$ of 79% in preterm infants during the first day after birth. $^{30}$ This is in line with our study. Several other studies found $r_3SO_2$ values <70% and FTOE values of approximately 0.30 during the first days after birth. $^{13,20,28}$ Another study showed a mean $r_3SO_2$ value of 66% in 10 preterm infants >7 days of age at the time of receiving mechanical ventilation. $^{31}$ Compared with these studies, the $r_3SO_2$ values of the infants in our study were somewhat higher. Nonetheless, we did find differences of approximately 10% ($r_3SO_2$) and approximately 0.10 (FTOE) between infants with and without GMH-IVH or PVHI.

We recognize several limitations to our study. In this study, we did not measure CBF directly. Cranial ultrasound scans that measure Doppler flow velocity in cerebral arteries, before and after measuring $r_3SO_2$, might have yielded more information about CBF. Previous Doppler ultrasound studies, however, revealed conflicting results regarding the association between cerebral perfusion and risk of GMH-IVH.$^{3,2}$ In addition, Doppler flow velocities correlated poorly with CBF measured by $^{131}$Xenon clearance. $^{33}$ Another limitation was the limited number of severe hemorrhages. Nevertheless, we even found differences in $r_3SO_2$ and FTOE in infants with a mild GMH-IVH, or even Grade I GMH. Although it might be that the lower cerebral oxygenation in preterm infants who had a mild GMH-IVH is a random observation due to the post hoc nature of our study design, this finding is intriguing and requires further study. We have yet to find out whether this is also relevant for neurobehavioral outcome. A recent study did report that extremely low birth weight infants with Grade I and II GMH-IVH have a poorer neurodevelopmental outcome at 20 months corrected age compared with infants with normal cranial ultrasound scans.$^{34}$

**Conclusion**

Preterm infants with GMH-IVH or PVHI had lower $r_3SO_2$ and higher FTOE during the first 2 weeks after birth irrespective of the grade of GMH-IVH. This suggests that cerebral perfusion is decreased persistently for 2 weeks in infants with GMH-IVH, even in the presence of mild hemorrhages.

**Acknowledgments**

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**Disclosures**

None.

**References**


Cerebral Oxygenation in Preterm Infants With Germinal Matrix–Intraventricular Hemorrhages

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