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ORIGINAL ARTICLE

# Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants

**H Fuchs, W Lindner, A Buschko, M Almazam, HD Hummler and MB Schmid**

*Division of Neonatology and Pediatric Intensive Care, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany*

**Objective:** To explore if regional cerebral tissue oxygen saturation monitoring by near-infrared spectroscopy (NIRS) is feasible during neonatal resuscitation of very low birth weight (VLBW) infants after birth.

**Study Design:** Cerebral tissue oxygen saturation was measured by NIRS in 51 VLBW infants (mean gestational age: 27.8 weeks) during the first 10 min after delivery.

**Result:** A regional cerebral tissue oxygen saturation signal was available after a median (interquartile range) age of 52 (44 to 68) s. In three infants the signal was obtained after 10 min of age. After delivery cerebral tissue oxygen saturation rose continuously from 37 (31 to 49) % at 1 minute of age and reached a steady state in the range of 61 to 84% ~7 min after birth. Percentiles of cerebral tissue oxygen saturation of this cohort of preterm infants are given.

**Conclusion:** Cerebral tissue oxygen saturation monitoring is feasible during neonatal resuscitation of VLBW infants within the first minutes of life.

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**Keywords:** cerebral oxygenation; near-infrared spectroscopy; very low birth weight infant; pulse oximetry; cerebral blood flow

## Introduction

Pulse oximetry during neonatal resuscitation is more accurate in estimating arterial oxygen saturation ($SpO_2$) and heart rate in very low birth weight (VLBW) infants compared with clinical assessment relying on the infants skin color, auscultation of the heart rate and palpation of the infants' pulses.[1,2] Therefore, monitoring of $SpO_2$ and heart rate by pulse oximetry are recommended during resuscitation of preterm infants.[3,4] Heart rate and $SpO_2$ allow clinicians to judge successful transition and help to guide interventions to support this process. In addition, accurate measurement of $SpO_2$ is the prerequisite to adjust inspired oxygen concentrations to avoid either hypoxia or hyperoxia.[5,6]

However, delivery of oxygen to distant organs depends not only on sufficient $SpO_2$ but also on adequate blood pressure, cardiac output, organ perfusion and sufficient oxygen transport capacity. Assessment of these parameters is difficult in the first minutes of life in VLBW infants where invasive measures are not possible. Therefore, clinical signs such as skin color, capillary refill time or palpation of pulses are used in clinical practice to estimate hemodynamics of the newborn infant.

Near-infrared spectroscopy (NIRS) is a technology that allows non-invasive continuous real time measurement of the regional tissue oxygen saturation of distant organs. It has been used in preterm infants for various healthcare conditions such as respiratory distress syndrome,[7] red blood cell transfusion,[8] desaturations,[9] indomethacin therapy[10,11] or ligation of a patent ductus arteriosus[12,13] and during the critical first days of life.[14–17] Major determinants of the regional tissue oxygen saturation are changes in $SpO_2$, regional perfusion, regional blood volume and metabolic rate of oxygen utilization.[18,19] Cerebral tissue oxygen saturation (cerebral $StO_2$) correlated well with superior vena cava flow and left ventricular cardiac output in preterm infants in the first days of life.[20,21] Therefore, continuous monitoring of cerebral oxygenation may be an ideal tool to detect a state of low cerebral-oxygen delivery in preterm infants during neonatal resuscitation.

We hypothesized that measurement of cerebral tissue oxygenation by NIRS is feasible in VLBW infants immediately after delivery, and thus may be useful for monitoring and to detect adverse conditions during the critical postnatal phase of transition to extrauterine life.

## Methods

### *Subjects*

Infants <1500 g who were born between December 2009 and February 2011 at the University Medical Center Ulm were included in this study if a research team member was present during delivery who was not involved in the resuscitation of the infant.

Correspondence: Dr H Fuchs, Division of Neonatology and Pediatric Critical Care, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm University, Eythstr. 24, 89075 Ulm, Germany.
E-mail: hans.fuchs@uniklinik-ulm.de
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The team member assisted to apply the sensor, activated the device and was responsible for documenting the event flow. The study was approved by the local ethics committee (Ethikkommission University of Ulm; No. 49/08; 01/11) and informed consent was obtained before or after delivery in agreement with the decision of the Ethics committee.
Direct impact of sustained inflations on cerebral oxygenation from a subgroup of this cohort of preterm infants has been reported elsewere.[22]

*Neonatal resuscitation*
Neonatal resuscitation was performed according to a standardized protocol: resuscitation was performed under an overhead heater and infants were placed into a plastic bag to avoid heat loss. A laser sensor utilizing four different wavelengths for cerebral $StO_2$ monitoring (FORE-SIGHT, Casmed, Branford, CT, USA) was attached at the infants' forehead. The sensor was fixed accurately with cohesive conforming bandage (Peha-haft, Hartmann, Heidenheim, Germany). In very immature infants a sterile glove was interposed between sensor and skin. Further, sensors for pre- and postductal pulse oximetry (Radical Software Version 7.0.3.3, Masimo, Irvine, CA, USA) were applied to the right hand and left leg. If necessary, excessive secretions were suctioned from the mouth. Thereafter, the infants were stimulated. If respiratory support was indicated because of low respiratory effort a nasopharyngeal tube was inserted 3 to 4 cm into one nostril and nasal continuous positive airway pressure was applied at 5 cm $H_2O$ at $FiO_2$ 0.4 using a F120 neonatal ventilator (Stephan, Gackenbach, Germany). If the heart rate remained below 100 bpm or $SpO_2$ remained <70% without increase, up to three sustained inflations were applied for lung recruitment at increasing pressures (20, 25, 30 cm $H_2O$) for 15 s each, followed by nasopharyngeal intermittent mandatory ventilation or nasal continuous positive airway pressure as described before.[23,24] $FiO_2$ was adjusted to maintain $SpO_2$ at 80 to 92%. Infants were intubated in the delivery room if the heart rate remained below 100 beats per minute or if their oxygen need remained above 40%. Following standard protocol chest compressions would have been applied for persistent bradycardia after intubation.

*Data analysis*
Serial data of the Radical pulse oximeters and the FORE-SIGHT cerebral oximeter were simultaneously recorded in 2 s intervals. Percentiles for cerebral $StO_2$, $SpO_2$ and heart rate were fitted by polynomial regression analysis of the raw data. Fractional tissue oxygen extraction (FTOE) was calculated using the formula: ($SpO_2$-cerebral $StO_2$)/$SpO_2$. Data were analyzed using analysis of variance or analysis of variance on ranks for repeated measurements. Data were analyzed with SigmaStat (Systat Software, San Jose, CA, USA).

## Results

Clinical details of study infants are given in Table 1. Cerebral $StO_2$ after delivery was low with a median of 37 (31 to 49)% at 1 minute ($n = 34$ infants) and continuously rose reaching a steady state of 61 to 84 % ~7 min after birth (Figure 1a). Percentiles of cerebral $StO_2$, preductal $SpO_2$, heart rate and FTOE are shown in Figure 1a–d, respectively. Heart rate and $SpO_2$ reached a steady state before cerebral $StO_2$. Relative changes of median heart rate and $SpO_2$ in relation to cerebral $StO_2$ and FTOE are shown in Figure 2a for comparison.

Very low and negative FTOE values were found at low $SpO_2$ as measured by pulse oximetry (Figure 2b).

In most infants ($n = 41$; 80%) the application of sustained inflations followed by nasal intermittent mandatory ventilation was necessary for stabilization. Ten infants had very good respiratory effort, therefore no respiratory support or simple nasal continuous positive airway pressure was applied. Cerebral $StO_2$, heart rate and $SpO_2$ of these infants were similar to infants needing more aggressive support of respiration (Figure 3a). In two infants who developed intraventricular hemorrhage cerebral $StO_2$ measurements were below the 10th centile (Figure 3b).

Median time from birth to availability of the cerebral $StO_2$ signal was 52 (44 to 68) s. This was before the pulse oximeter signal was available ($P<0.001$). Median time from birth to availability of the pulse oximetry signal was 74 (62 to 94) s for the preductal and 85 (66 to 113) s for the postductal pulse oximeter

**Table 1** Characteristics of infants

| | *All study infants (n = 51)* | *Infants without respiratory support or with nCPAP only (n = 10)* |
|---|---|---|
| Gestational age (weeks)[a] | 27.8 (2,6) | 29.1 (2.7) |
| Birth weight (g)[a] | 913.3 (298) | 1119 (226) |
| Male | 25 (49%) | 5 (50%) |
| Intrauterine growth restriction | 15 (29%) | 1 (10%) |
| Premature rupture of membranes (>24 h) | 9 (18%) | 2 (20%) |
| Full course of steroids | 39 (76%) | 7 (70%) |
| Cesarean section | 47 (92%) | 8 (80%) |
| Apgar score at 1 min[b] | 6 (4–6) | 8 (7–9) |
| Apgar score at 5 min[b] | 9 (8–9) | 10 (9–10) |
| Apgar score at 10 min[b] | 10 (9–10) | 10 (10–10) |
| Cord pH[a] | 7.31 (0.11) | 7.37 (0.05) |
| Number of sustained lung inflations[b] | 2 (1–2) | — |
| Intubation in delivery room | 7 (14%) | — |

Abbreviation: nCPAP, nasal continuous positive airway pressure
[a]Mean (s.d.).
[b]Median (interquartile range).

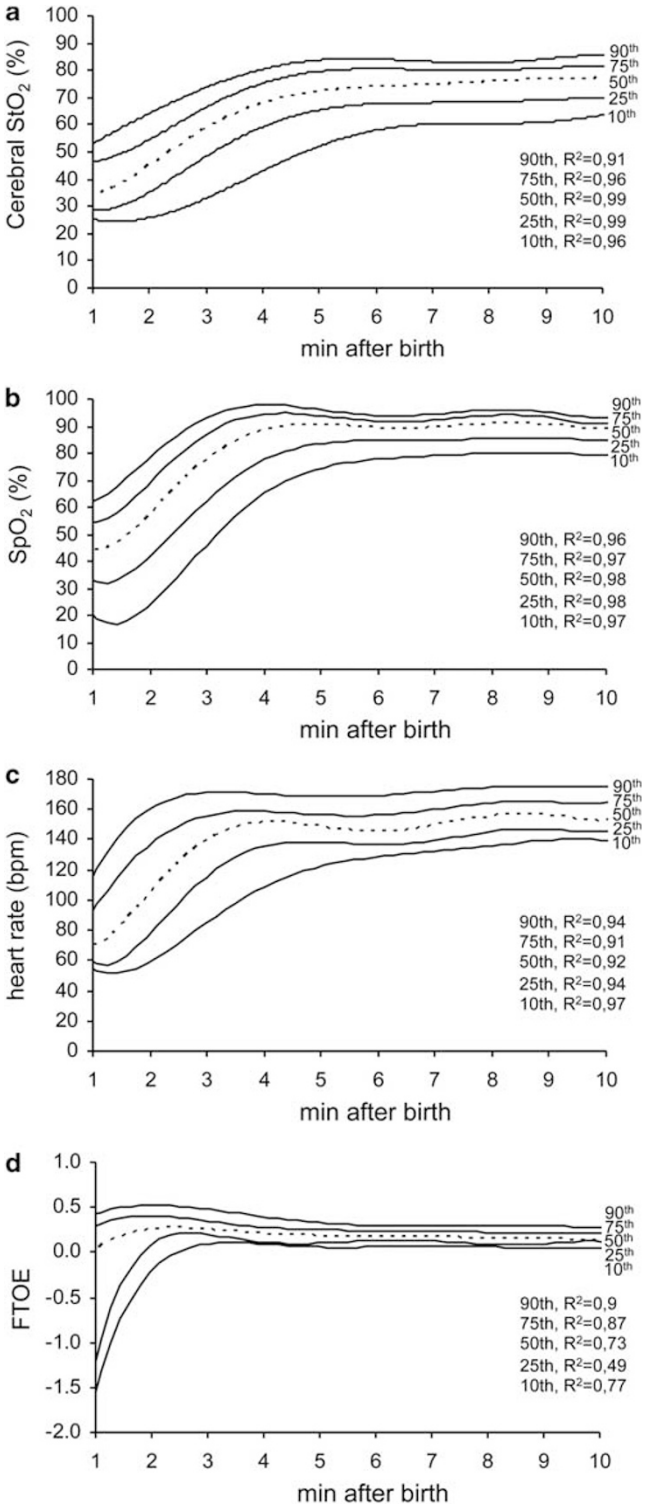


**Figure 1** Changes in cerebral and arterial oxygen saturation and heart rate in very low birth weight infants after birth. The 10th, 25th, 50th, 75th and 90th percentiles are given of cerebral $StO_2$ (**a**), preductal $SpO_2$ (**b**), heart rate (**c**) and fractional tissue oxygen extraction (FTOE, **d**) in the first 10 min after birth.

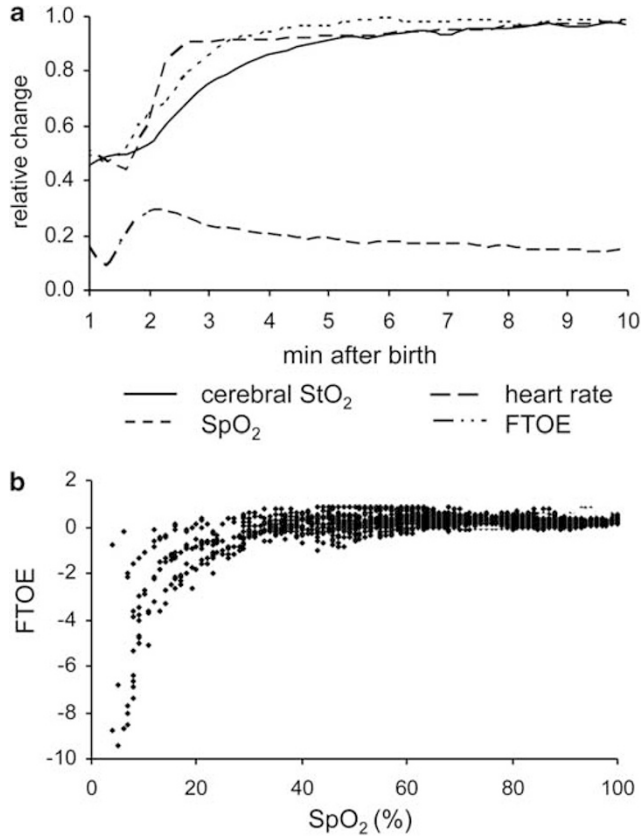


**Figure 2** Relative changes of parameters of interest and fractional tissue oxygen extraction (FTOE) in relation to $SpO_2$. (**a**) Relative changes of the medians of cerebral $StO_2$, heart rate, $SpO_2$ and FTOE. (**b**) FTOE in relation to $SpO_2$.

(Figure 4). The cerebral $StO_2$ trace was temporarily lost in 15 infants for 120 (64 to 208) s and in three infants no cerebral $StO_2$ trace was available in the first 10 min of life. The preductal pulse oximeter signal was lost temporarily in 11 infants, no signal was available in one infant in the first 10 min of life and the postductal pulse oximeter signal was temporarily lost in 15 infants.

## Discussion

NIRS is used to monitor cerebral oxygenation non-invasively. It may be helpful to detect a state of low cerebral perfusion and clinical applications so far include cardiac surgery,[25] extracorporeal membrane oxygenation[26,27] and brain injury[28] in more mature infants and children. Applications in preterm infants included cerebral monitoring during the first days of life[7,14,20] or during therapy of a patent ductus arteriosus.[11,13] We tested, if monitoring of cerebral $StO_2$ is feasible in VLBW infants during neonatal resuscitation during the first minutes after delivery.

In our study, at the age of 1 minute the range of cerebral $StO_2$ was 31 to 49% and increased to a steady state of 61 to 84% ~7 min after birth. The increase in cerebral $StO_2$ was preceded by

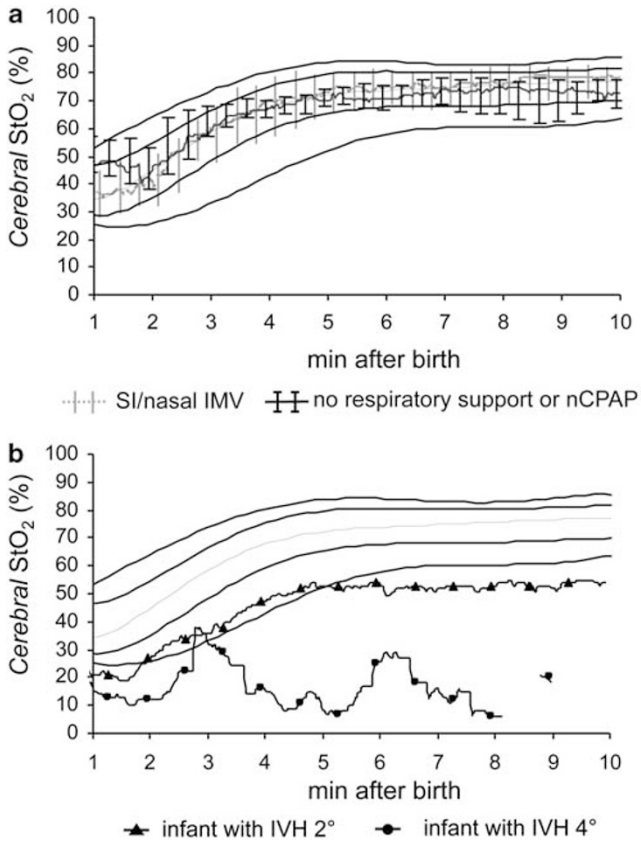


**Figure 3** Cerebral $StO_2$ according to measures for respiratory support and intraventricular hemorrhage. (**a**) Infants where sustained inflations, nasal intermittent mandatory ventilation or invasive ventilation were used for resuscitation were plotted against infants where no respiratory support or only nasal continuous positive airway pressure (nCPAP) was used. Medians (interquartile range) are plotted on the percentiles of the cohort. (**b**) The two infants that subsequently developed intraventricular hemorrhage had low cerebral $StO_2$ levels in the first 10 min of life.

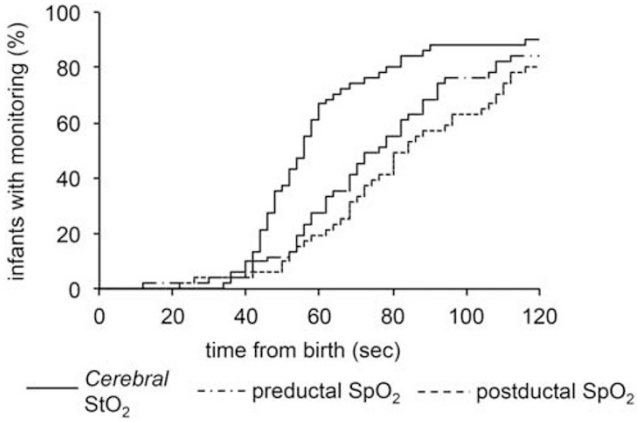


**Figure 4** Time from birth to monitoring. The proportion of infants with successful monitoring of cerebral $StO_2$, preductal and postductal $SpO_2$ is shown.

an increase in heart rate and $SpO_2$. The time until steady state cerebral $StO_2$ was reached was several minutes longer than expected by the increase in heart rate and $SpO_2$. After delivery, the infants' heart has to adapt to major changes in hemodynamics. After cutting the umbilical cord the systemic vascular resistance increases. Concomitantly pulmonary vascular resistance decreases resulting in increased blood flow through the lungs, increased pulmonary vascular return and increased left atrial preload.[29] We speculate that the relatively slow increase in cerebral $StO_2$ may reflect adaptation of the heart to these changes until normal cerebral blood flow is reestablished.

Previously, cerebral $StO_2$ measurements beginning at 3 min of life were reported in healthy term newborn infants with no need of respiratory support after elective Cesarean section.[30,31] The range of cerebral $StO_2$ observed during spontaneous transition of these infants was similar to the range of cerebral $StO_2$ that we observed in our VLBW infants despite their immaturity and their need for supportive measures. However, the steady state in these infants were slightly lower than the values observed in the VLBW infants.[30,31] Higher values of cerebral $StO_2$ in preterm infants compared with full term infants in the first days of life have been observed in another study. It had been speculated, that this may be related to elevated $PCO_2$ resulting in increased cerebral perfusion in the immature infants.[32] $PCO_2$ may be elevated temporarily during transition.[33] This may explain the higher values observed. However, direct comparison of our data to the data of the full-term infants must be interpreted cautiously as different devices were used, which may influence absolute values.

Similar to the studies in term infants the majority of VLBW infants in this study were delivered by Cesarean section. It reflects the policy of our center to deliver VLBW infants by cesarean section using spinal anesthesia if the delivery at presentation has not yet advanced into second stage. However, there is controversy over how this strategy may affect the outcome.[34]

Most VLBW infants need respiratory support including additional oxygen, nasal continuous positive airway pressure or mechanical ventilation during transition after birth.[35] Clinical assessment of the infants by observation of skin color and palpation of pulses still is a mainstay during neonatal resuscitation of preterm infants and guides the measures taken to stabilize the infants in the first minutes. However, there is large interobserver variability in assessing the infants color[1] and palpation of the infants pulses underestimates the infants heart rate.[2] Therefore, monitoring of the $SpO_2$ and of the heart rate by pulse oximetry is recommended.[3,4] There is still controversy regarding the reference range for $SpO_2$ and heart rate measured by pulse oximetry in the first minutes after birth. In addition, there are no studies to show that measuring $SpO_2$ and heart rate in the delivery room improves infant outcomes.[36] Nevertheless, pulse oximetry now is used in most centers in the delivery room and has become the standard monitoring tool during delivery room care.[37]

Normal range measurements of pulse oximetry do not necessarily indicate adequate delivery of oxygen to distant organs. Low cardiac output, low blood pressure or severe anemia may cause low tissue oxygenation in sick preterm infants after birth.[29] However, in the delivery room clinical recognition of these conditions may be even more difficult compared with detection of hypoxia or bradycardia. Exact evaluation of hemodynamics usually requires invasive measures that are not feasible during the first minutes of life.

NIRS allows monitoring of tissue oxygenation of distant organs.[38] This method is non-invasive and allows continuous real time monitoring at the bedside. Cerebral $StO_2$ represents the mixed oxygen saturation in a multicompartmental system of arteries, arterioles, capillaries, venules, and veins[18,26] and is affected by several factors: $SpO_2$, blood flow, blood volume and oxygen consumption of the organ of interest.[38]

Therefore, NIRS may close the gap of monitoring cardiac output and organ perfusion. As the brain is the most fragile organ in the newborn premature infant, brain oxygenation monitoring may be helpful in recognizing low brain perfusion and preventing potential sequelae.

We found that cerebral $StO_2$ monitoring was successful in most VLBW infants within seconds after the sensor was applied. The cerebral $StO_2$ signal was often detected earlier than the signal of the pulse oximeters. However, there may be some bias, because the sensors were not always attached at exactly the same time. In some infants there was a slight delay in attachment of the postductal $SpO_2$ sensor. Measurements were more difficult in more immature infants as the cerebral $StO_2$ signal was first detected 10 min after birth in three infants $<25$ weeks gestation. Nevertheless, in four infants $<25$ weeks gestation the cerebral $StO_2$ signal was obtained in 48 to 53 s.

Pulse oximetry calculates $SpO_2$ from the variable light loss due to pulsations and eliminates the constant light loss from surrounding tissues. Therefore, pulsating blood flow is crucial for pulse oximetry and in situations of low perfusion, pulsations may be too low to be detected accurately and the pulse oximeter may detect no signal or even give false readings.[39] In contrast, cerebral $StO_2$ is measured in all compartments of the vascular system; therefore, it is not dependent on blood flow pulsations. However, interferences of ambient light may cause false readings. We rarely observed obvious artifacts of cerebral $StO_2$. However, the trace was lost secondary in several infants because of sensor dislocation. This was most likely to occur if a nasopharyngeal tube was inserted or if the infant was intubated. Accurate fixation of the sensor and cautious attention of the clinical team not to dislocate the sensor therefore is a prerequisite for stable measurements.

At normoxia the arterial compartment contributes $\sim 30\%$ of cerebral $StO_2$, whereas 70% is derived from the venous compartment.[26] At hypoxia this ratio might change with an increase in the arterial compartment, eventually due to vasodilation of the arterial system and inhomogeneous changes of regional cerebral blood flow.[18] However, cerebral $StO_2$ exceeding $SpO_2$ and resulting in a negative FTOE as found in our study at very low $SpO_2$ is impossible. In addition, it is unlikely that a heart beating at $<100$ beats per minute could supply blood flow to the brain to the extent that a FTOE is lower than normal. Most likely these phenomena represent artifacts related to inaccurate calibration of the pulsoximeter and/or the cerebral oximeter at low saturation values. For pulse oximeters it is known that accuracy decreases at $SpO_2$ below 75%.[40,41] Cerebral $StO_2$ values have been validated in humans to cerebral tissue saturations of 50%.[42] However, one study suggests a trend for overestimation at very low values.[26] Therefore, absolute numbers of both very low arterial and very low cerebral tissue oxygen saturation and the FTOE calculated from low saturations must be interpreted with great caution.

Even given this limitation, observing time evolution of relative values may prove to be useful for monitoring in the delivery room. During neonatal resuscitation it may help to identify infants with low brain tissue oxygenation due to poor cerebral perfusion. Monitoring of brain oxygenation also may help to titrate supplemental inspired oxygen independent from $SpO_2$, if brain oxygenation is adequate. We observed similar values of cerebral $StO_2$ in infants with good respiratory effort and infants with low respiratory effort that had ventilatory support. However, further studies are needed to define adequate ranges of cerebral tissue oxygen saturation and to examine to what extend cerebral $StO_2$ monitoring in the delivery room may guide interventions during transition.

Low cerebral blood flow as measured by superior vena cava flow[43,44] or NIRS[14–16] in the first days of life is known to be associated with adverse neurological outcome and intraventricular hemorrhage. There are no data, as to whether this applies also during the immediate period of neonatal resuscitation. Interestingly, in the two infants who later developed intraventricular hemorrhage we observed a cerebral $StO_2$ below the 10th percentile after birth. This may indicate that impaired cerebral blood flow was already present in these infants in the delivery room.

Evaluation of hemodynamics including arterial blood pressure measurement and functional echocardiography in the sick preterm infant may be difficult in the delivery room, where other life supporting measures such as intubation, surfactant delivery or catheter insertion also have a high priority. Therefore, an easy-to-apply non-invasive monitoring system that provides information on tissue oxygenation and perfusion would be a helpful tool in the future. Nevertheless, further research is needed to identify thresholds of cerebral $StO_2$ for an increased risk for adverse outcome, and to guide interventions.

In conclusion, we have shown that cerebral oximetry is feasible within 1 to 3 min after delivery in VLBW infants. However, further studies are needed to define normal ranges of cerebral $StO_2$, to understand the impact of early cerebral $StO_2$ on outcomes and to explore the usefulness of interventions guided by this new method during the transitional period after delivery.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgments

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