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TESI DI DOTTORATO IN

Ventilatory Support, Extubation and Cerebral Perfusion Changes in Preterm: a NIRS study

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1. Introduction

The survival of premature infants has significantly improved over the years and from the mid-90s to the present there has also been an improvement in the neurological outcome[1].

The alteration in the psychomotor development of the preterm patient is due to numerous factors, a fundamental role being played by brain injuries.

Germination matrix haemorrhage (GMH) and intraventricular haemorrhage (IVH) are by far the most frequent lesions in patients younger than 33 weeks with an incidence ranging from 15 to 20% depending on the populations described and arrives up to 30-40% in patients with extreme prematurity (<28 weeks) [2]. They are typical lesions of the first week of life, particularly in the first 72 hours, and present various complications such as post-hemorrhagic hydrocephalus and periventricular venous infarction which have a particular impact on the neuro-cognitive prognosis of preterm patients[3] .

Risk factors for intraventricular hemorrhage include prenatal factors such as non-occurrence of steroid prophylaxis, perinatal factors such as the mode of delivery and postnatal factors in particular the instability of oxygenation and cerebral flows secondary to factors such as arterial hypotension which requires therapy with inotropes and intravenous fluids or sudden changes in CO2 levels due to changes in ventilation mode or the presence of a significant patent ductus arteriosus[4]. Changes in intracranial venous pressure are also a risk factor for haemorrhage and these can be caused by an increase in intrathoracic pressure, secondary to invasive ventilation, CPAP, or diseases such as pneumotorax[5] [6].

Recognition of these risk factors is essential for rapid intervention capable of preventing bleeding events. Vital signs such as peripheral saturation, blood pressure and heart rate are important to monitor the clinical condition of the newborn but not provide direct data on oxygenation and cerebral flow. This data can be provided by NIRS.

1.1 Near-InfraredSpectroscopy (NIRS)

Near-infraredspectroscopy (NIRS) is a tool that allows continuous and non-invasive monitoring of oxygen saturation at the tissue level (rSO2). The technique is based on the principle of relative transparency of biological tissues to light regulated by the law of Lamber and Beer:

$$I = I_0 e^{-\mu_a \Delta}$$

I *I0* is the intensity of the light at the source; I is intensity of the light after crossing a distance D in a medium with an absorption coefficient μa.

The near-infrared light radiation (near-infrared or NIR, 700-1000 nm) emitted by the instrument penetrates the tissue and passes through it forming a semi-curve for approximately 2-3 cm in depth[7] (Fig. 1). Oxygenated (O2Hb) and deoxygenated (HHb) hemoglobin absorb radiation at different wavelengths, the differences in absorption are recorded by a sensor and allow to calculate the levels

of O2Hb and HHB from which the rSO2 derives. Unlike the pulse oximeter, which measures the oxygen saturation in arterial blood, the provided by NIRS is a combination of arterial and venous blood saturation in a determined fabric with a ratio of about 25:75 respectively [8]. There is therefore a large contribution of the venous component in the value of rSO2 and this has been demonstrated by observing the correlation between cerebral rSO2 and the bloody measurement of O2 saturation at the level of the jugular vein[9] .

The sensors most commonly used for measuring NIRS consist of a continuous light NIR radiation emitter and two or more receivers capable of distinguishing between signal attenuation due to more superficial tissues and that due to deeper tissues, in particularly the cerebral cortex, reducing the influence of light scattering on the captured signal[10] . There are numerous types of sensors on the market that evolve over time with particular attention to pediatric and neonatal use which requires small dimensions and particular flexibility of materials. These changes made necessary for clinical use, however, highlighted some differences in the results of rSO2 if we compare sensors designed for pediatric and neonatal use with those designed for use in adults with cerebral rSO2 values greater than 10 to 14% when using a sensor neonatal [11].

Near infrared spectroscopy (NIRS) is a potential tool to monitor the haemodynamic status in neonatal brain. This technology can allow for continuous and non-invasive monitoring of cerebral tissue oxygenation (rScO2), even in most vulnerable infants[12]. Starting from cerebral rSO2 and peripheral saturation (SpO2), it is possible to calculate the cerebral fractional tissue oxygen

extraction (cFTOE) which is a better index of cerebral blood flow than rScO2, especially in case of low arterial oxygen levels (SpO2) [13].

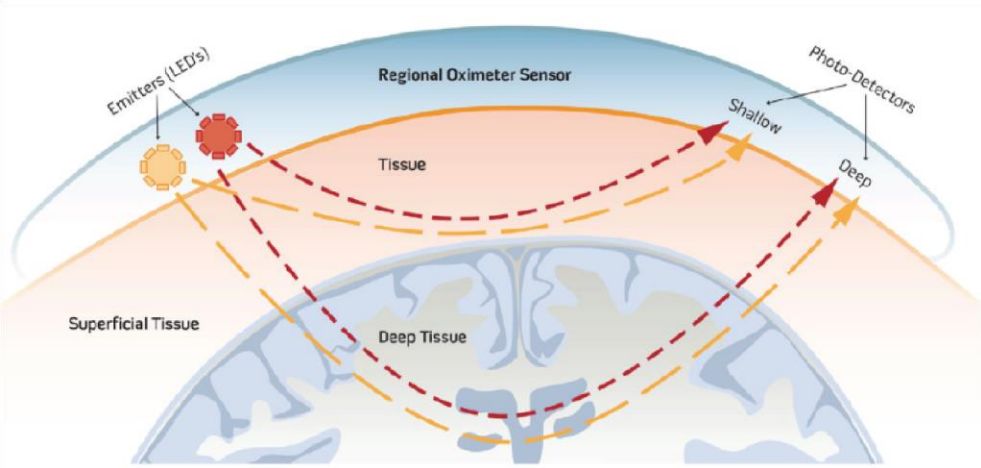

Figure 1: operating scheme of the NIRS. The figure shows well that there are 2 receivers, one that collects a very superficial signal that does not reach the cerebral cortex and a deep one. The set of the two processed signals will then give the rScO2 value.

The most common application of NIRS is the assessment of cRSO2 using sensors placed on the patient's forehead[14] . cRSO2 derives mostly from the balance between oxygen delivery and utilization in the gray matter in the frontal region. It is recommended that the cerebral probe be placed on the right or left side of the forehead and away from nevi, sinus cavities, the superior sagittal sinus, subdural or epidural hematomas, or other anomalies such as arteriovenous malformations. Bilateral cRSO2 monitoring can theoretically detect differential perfusion or oxygenation between hemispheres and particularly important in patients without an intact Circle of Willis, which occurs in 5% of neonates[15]. Because of the small surface area available on the

forehead, the midline position has been used successfully for monitoring cRSO2 in preterm neonates[16]. Factors that affect the accuracy of cRSO2 measurements include sensor placement at different locations on the forehead, shape of the forehead, extracranial structures and blood flow, and depth of the brain surface.

In neonates and infants, NIRS-measured RSO2 of deeper organs [kidneys (rRSO2), intestines (sRSO2)] is feasible due to their superficial location. In addition, peripheral tissue oxygenation (pRSO2) can be measured over the forearm, calf, upper arm, and upper leg. Placement of sensor over fatty deposits, hair, bony protuberances, nevi, hematomas or broken skin, or application of pressure to the sensor may result in inaccurate readings.

Transcutaneous NIRS is non-invasive and the light intensities are not harmful to the tissue, typically not causing skin burns even if applied for a longer period[17 18].

1.2 NIRS application

The introduction of NIRS as a monitoring technique in clinical use dates back to about 40 years ago but only in the last decade does its popularity seem to have grown within the pathology and neonatal intensive care departments. Of particular interest is the monitoring of rSO2 at the cerebral level (rScO2) which allows for real-time data on the state of oxygenation and cerebral perfusion [19].

The normal values of rScO2 vary in the newborn according to the postnatal age and are still under study. Immediately after delivery, they are around 40-56% regardless of the mode of delivery, they increase up to 78% in the first 24-48 hours and then stabilize on values between 55% and 85%. [20].

More information about the extraction of oxygen by the brain tissue is provided by the fraction of tissue oxygen extraction (FTOE or cFTOE if referred to rScO2) calculated starting from the value of rSO2 and from the peripheral SpO2 ((SpO2-rSO2) / SpO2). This parameter correlates with the fraction of oxygen extraction (FOE) measured in an invasive way in newborn pigs[21] and is a better parameter than rScO2 for assessing the state of perfusion in the brain, particularly in the case of in front of low arterial SpO2 levels or support with exogenous O2 as often happens in preterm infants with pulmonary or cardiac pathology since it is independent of SpO2 and therefore also of FiO2 supplied to the newborn [13]. Furthermore, this parameter is very useful for evaluating the mechanisms of self-regulation of cerebral flow when correlated with systemic arterial pressure [22].

The clinical and prognostic significance of rScO2 monitoring is still being defined. Regarding adults, there are studies showing that values of less than 50% of pre-operative rScO2 and frequent intraoperative desaturations in patients undergoing cardiac surgery correlate with high mortality and cognitive damage [23].

In the neonate, it has been observed that rScO2 can be predictive of neurological outcome in term patients with peripartum hypoxic ischemic encephalopathy [24] and in preterm life low rScO2 and / or elevated cFTOE levels were associated in the first days with intraventricular haemorrhage [25] [26], moreover, a worse neurological outcome was associated with rScO2 values <50% for more than 10% of the time in the first 72 hours of life[27] .

Cerebral oximetry is widely used in the management of neonates undergoing cardiac surgery[28] [29]. A good correlation between cRSO2 and jugular venous bulb oxygen saturation (SjvO2) has been reported in children with CHD and in animal studies[15]. Simultaneously measured rRSO2 can serve as a control for cRSO2 by differentiating changes in total-body perfusion from selective changes in cerebral perfusion and metabolic activity.

Normative RSO2 data for healthy term newborns has been described in a small number of reports with small sample sizes based on short recordings in the first few days of life[30].

The healthy newborn has significantly different ranges of cRSO2, rRSO2, and sRSO2 values than those seen in pediatric and adult patients; in addition, values evolve over time. In a cohort of 26 healthy term neonates with an average age of 44 ± 28 h, average cRSO2 was 77.9% ± 8.5% [95% confidence intervals (CI): 64% to 89%] and rRSO2 was 86.8% ± 8.1% (95% CI: 75% to 97%) [30]. Over the first 120 h after birth, average cRSO2 decreased ($P < 0.01$), and rRSO2 remained unchanged.

NIRS has been used for monitoring cRSO2 in neonates during transition after birth, a period when the brain is vulnerable to injury and dysfunction[31]. In term infants at birth, cRSO2 rapidly adapts to extrauterine life with values of 44% at 3 min to 76% at 7 min, after which it remains stable[32] cRSO2 achieves a plateau earlier than pulse oximetry (SpO2) or pRSO2[31].

These results demonstrate the potential for preferential oxygen delivery to the brain with increasing cerebral blood flow in the first minutes after birth. Although significantly lower SpO2 and heart rate values have been reported in infants born by cesarean section[32] in the first 8 min

after birth, cRSO2 was not affected by manner of birth, indicating that blood flow to the brain is possibly determined by autoregulation independent from the mode of delivery[31]. Interestingly, cRSO2 of vaginally delivered neonates shows a decrease of up to 10% accompanied by an increase of cerebral FTOE (cFTOE) after 8 min of age. NIRS monitoring is becoming widely used in premature newborns as it has the potential to provide valuable insights on the impact of prematurity and intensive care on early brain development [33]. The normal reference range of cRSO2 for preterm infants varies between 55% and 85% depending on multiple factors such as instrument design, clinical status, and postnatal age[34] . cRSO2 in the first day of life was higher and cFTOE lower in healthy, very preterm infants in stable condition, compared with healthy term newborns[35] .There was no significant correlation between head size and cRSO2. Tina et al. reported cRSO2 and cFTOE in the first 6 h after birth in100 healthy newborns, 30 and 42 weeks' gestation[36]. A significant negative correlation between cRSO2 and gestational age was found (r ¼ 0.77; P < 0.001). Highest cRSO2 and the lowest cFTOE (P < 0.001, for all) were found at 30 and 33 weeeks; thereafter, cRSO2 progressively decreased and cFTOE increased, reaching their lower nadir/peak respectively (P < 0.001, for all) at 38 and 39 weeks. cRSO2 also correlated significantly with heart rate, respiratory rate, and SaO2 values (r ¼ 0.65; P < 0.001). Moreover, cRSO2 values were significantly higher (P < 0.01) after cesarean section compared to vaginal delivery.

NIRS has been used to monitor cRSO2 in HIE[33]. In neonates with HIE, cRSO2 was significantly higher between 24 and 48 h of age in neonates with adverse outcomes as compared to those with

favorable outcomes, suggesting a decrease in cerebral oxygen consumption during secondary energy failure[37]. These findings were validated in a newborn piglet asphyxia model[38]. Newborns with evidence of hypoxic ischemic brain injury on MRI have higher cRSO2 than newborns without brain injury. Cerebral autoregulation, a complex developmentally regulated process affected by multiple pathophysiologic factors, is absent in 40% of preterm neonates[39]. Absence of cerebral autoregulation in preterm infants is associated with adverse outcomes[40]. High coherence between mean arterial blood pressure and cRSO2 indicates cerebral pressure passivity and impaired cerebral autoregulation in clinically sick preterm infants, and is strongly associated with subsequent intracranial hemorrhage or mortality[40] [41].Verhagen et al. used correlation between cFTOE and MABP to predict cerebral autoregulation, suggesting a role for NIRS to guide interventions to improve cerebral circulation[42].Although NIRS has been used extensively to study cRSO2, there are fewer reports about the use of NIRS to monitor sRSO2 to predict necrotizing enterocolitis (NEC) and to guide decisions to initiate feeds. The use of NIRS to monitor sRSO2 has been perceived to be unreliable because of the changing gas and fluid surfaces and intraluminal fecal content[19]. It has been speculated that fecal chromophores, biliverdin and bilirubin, may interfere with sRSO2 measurements. The peak absorption spectra for these chromophores (455 nm for bilirubin and 660 nm for biliverdin) are very different from those utilized in the INVOS monitor, suggesting nominal interference with sRSO2 measurements.

1.3 NIRS Interpretation

To interpret the rScO2 values it is necessary to consider that cerebral oxygenation and perfusion are influenced by many variables, of a cardiocirculatory nature (arterial pressure, heart function and patency of the duct), respiratory (pCO2 and SpO2 levels, intrathoracic pressure), metabolic (blood glucose levels), hematological (hemoglobin levels). It should also not be forgotten that the monitoring is often affected by artifacts as the sensor must always be perfectly adherent to the skin, possibly shielded from external light through the use of bandages or caps and that even minimal movements of the sensor can lead to changes in rScO2 greater than 6%[43] .Now let's see in detail how the rScO2 values are changed based on some of the main ones preterm variables and what is the role of NIRS in evaluating these aspects:

Ventilation: the preterm infant often needs invasive or non-invasive respiratory support and the ventilation modes and parameters used play a fundamental role in oxygenation and cerebral perfusion. The rSO2 is closely related to the SpO2 values and consequently to the FiO2. It has been observed that following the increase in FiO2 in patients with episodes of apnea or desaturation, the rScO2 level tends to rise and remain more long increased with respect to peripheral saturation due to a probable phenomenon of acute reperfusion post hypoxia [44].

Cerebral flow is particularly influenced by the type of respiratory support provided to the newborn, particularly when non-invasive techniques such as continuous positive airway pressure (CPAP) and mechanical ventilation are compared[45] . Ventilation is the main regulatory mechanism of pCO2 which

is a powerful cerebral vasodilator and both hypocapnia and hypercapnia have been associated with brain damage and haemorrhage, an increase in pCO2 is reflected from the point of view of NIRS monitoring with an increase of rScO2 and a consequent reduction in tissue oxygen extraction (cFTOE) due to an increase in cerebral perfusion, while in the case of hypocapnia there will be the reverse effect [46]. Acute fluctuations in pCO2 even in a normal range could affect cerebral perfusion and consequently be associated with the presence of neurological damage especially intraventricular hemorrhage [47], these fluctuations are detectable with NIRS monitoring which allows rapid recognition and therefore would provide the clinician with additional data to optimally manage ventilation to maintain cerebral flow levels. As stable as possible and within the normal range. Other factors related to breathing can reduce cerebral oxygenation in particular apneas, increase in mean airway pressure during mechanical ventilation and respiratory distress syndrome (RDS) which also leads to greater instability of cerebral flow in the first three days of life and to increased risk of IVH. [48]

Patent ductus arteriosus: the significant patency of ductus arteriosus (PDA) is capable to negatively influence cerebral oxygenation due to a theft mechanism in particular in the presence of large PDAs with left-right shunt[49]. This phenomenon resolves after closure of the duct and this is reflected in the normalization of rScO2 values but prolonged exposure to low levels of rScO2 leads these patients to have a greater risk of reduced brain development[50] . Regarding the pharmacological treatment of the duct, it has been shown that Ibuprofen and Paracetamol do not seem to have a negative effect on cerebral perfusion and oxygenation as found with Indomethacin[51]. Furthermore, in patients undergoing surgical closure of the duct there is a higher incidence of prolonged periods of poor cerebral

oxygenation compared to patients treated with drug therapy[52] and this was associated with a worse neurological outcome and reduced cerebellar development [50].

Hypotension: the blood pressure values that define hypotension in the premature baby and the need for treatment are still under discussion, treatment with inotropes is not without side effects. Currently, the decision on treatment is mainly made on the basis of mean arterial pressure (MAP) associated with clinical signs of organ hypoperfusion such as refill, diuresis, blood gas analysis. NIRS can recognize organ hypoperfusion which is expressed with a reduction in rScO2 and an increase in the O2 extraction index (cFTOE). This data could help the clinician to suggest treatment with inotropes and monitor its effectiveness[53].

Cerebral self-regulation: defined as the ability to maintain cerebral perfusion and oxygenation stable during blood pressure fluctuations, this mechanism is essential to avoid cerebral hypoperfusion during hypotensive episodes. The rScO2 combined with the continuous monitoring of blood pressure is an excellent index for evaluating cerebral self-regulation [54]. In the event of loss of self-regulation mechanisms, rScO2 will passively follow the trend of blood pressure. This situation is found in extreme preterm infants in general and more particularly in some classic clinical conditions of the premature baby such as respiratory distress syndrome (RDS), the use of inotropes such as dopamine at high concentrations and surgical interventions[22]. The loss of self-regulation is associated with a impaired neurological outcome and brain injury and its timely recognition is therefore essential[40].

Anemia: the presence of anemia is reflected in the values evaluated by NIRS with a reduction in rSO2 and an increase in cFTOE compared to newborns with normal hemoglobin values. With the transfusion of concentrated red blood cells and the normalization of hemoglobin levels, the values of rSO2 and FTOE also normalize[55]. In this case, therefore, NIRS could offer a further data regarding the decision to transfuse a patient or not.

Hypoglycemia: hypoglycemia is very common in preterm births of low weight but is often asymptomatic and cannot be recognized without extemporaneous glycemic control. Prolonged low blood glucose values are associated with poor psychomotor development. NIRS monitoring can raise the suspicion of hypoglycemia in place as low blood glucose values are associated with an increase in cerebral flow and increased levels of rSO2 with a relative reduction in the index of O2 extraction[56].

1.4 GMH/ IVH and NIRS

Fluctuations in cerebral perfusion and poor cerebral oxygenation in the very first hours of life are risk factors for the development of intraventricular hemorrhage [25 26]. Other major studies have observed how patients who developed bleeding high-grade intraventricular vessels with parenchymal involvement had in the previous hours values of rScO2 and cFTOE correlated to cerebral

hyperperfusion, in particular this occurred in patients treated with inotropes that lead to a loss of self-regulation of cerebral flow[57]. NIRS monitoring also allows us to understand how brain oxygenation and perfusion change in patients who have already developed intraventricular or germinal matrix hemorrhage. In fact, it has been observed that in GMH / IVH patients the rScO2 values tend to be lower and the cFTOE values tend to be higher, as if the bleeding itself is able to modify cerebral perfusion and oxygenation [26]. This finding has been reported not only in the presence of high-grade bleeding but also in the presence of low-grade bleeding through advanced NIRS (frequency-domain near infrared spectroscopy and diffuse techniques)correlation spectroscopy; FDNIRS-DCS) capable of directly measuring perfusion and cerebral extraction of O2[58]. These alterations could partly explain how even in the presence of low-grade GMH / IVH and in the absence of complications, there is a worse neurological outcome than in preterm infants in the absence of hemorrhagic lesions.

Zhang et al. reported higher cRSO2 and lower cFTOE in the first 3 h after birth in preterm infants who later developed IVH compared to those who did not[59]. Alderliesten et al. reported higher cRSO2 and lower cFTOE in the 24 h before detection of P/IVH in very preterm infants monitored during the first 72 h of life[57]. In contrast, three investigators reported lower cRSO2 and or higher cFTOE in neonates with hemorrhage/IVH compared to those without [26]. There was a significantly negative correlation between the severity of IVH and cRSO2 (P ¼ 0.002).

Extubating a preterm baby is a challenging decision, especially during the first few days of life when there is a high risk of germinal matrix hemorrhage (GMH) intraventricular hemorrhage (IVH). GMH-IVH is the most frequent lesion affecting babies born before the gestational age (GA) of 34 weeks,

with incidence rates as high as 20%–30%[2] and variable outcomes. Most severe forms of GMH-IVH can affect neurological outcomes, also minor degree of hemorrhage may have a significant impact [60] [61]. Pathogenesis of IVH is multifactorial and closely linked to vascular immaturity within germinal matrix and fluctuation of cerebral blood flow [62] [63]. Preterm neonates with low GA typically exhibit impaired capacity for autoregulation of cerebral blood flow[22] [40]. These neonates are particularly sensitive to cerebral blood flow fluctuations especially in those with respiratory distress [4], pneumothorax [5], and those on mechanical ventilation, which is a known risk factor for GMH[6].

Early extubation is considered to improve neurological outcomes of preterm neonates[64]. Prolonged mechanical ventilation exposes the preterm infant to several adverse outcomes, including a higher risk of developing bronchopulmonary dysplasia [65] and neurodevelopmental impairment [66]. On the other hand, premature inappropriate extubation can cause lung derecruitment, compromise gas exchange, and increase respiratory fatigue necessitating reintubation [67]. Reintubation may potentially increase haemodynamic perturbations especially those affecting cerebral blood flow [68]. This phenomenon may potentially be aggravated by multiple attempts at reintubation, which is known to increase the risk of developing severe GMH-IVH[69].

The aim of the study is to evaluate how oxygenation (rScO2) and cerebral perfusion (cFTOE) levels change following the transition to invasive to non-invasive ventilatory support in premature patients in the first hours of life and compare changes in rScO2 and cFTOE during extubation based on the timing of extubation, check whether such changes in cerebral perfusion increase the risk of developing intraventricular haemorrhage.

2. Materials and methods: following Institutional Review Board approval as part of service evaluation, we reviewed all consecutive patients who were monitored using NIRS at our institution between October 2018 and October 2019. The inclusion criteria were: GA < 33 weeks, need for ventilatory support (either nasal continuous positive airway pressure [CPAP] or endotracheal tube [ETT]) at birth (within the first 5 hours of life); withdrawal of ventilatory support within the first 120 hours of life (*i.e.,* 5 days).The decision to stop the ventilatory support (*i.e.,* extubation) was in accordance with the institutional protocol based on ventilatory parameters, namely peak inspiratory pressure (PIP) ≤ 21 cm H_2O, positive end expiratory pressure (PEEP) ≤ 6 cm H_2O, a FiO_2 ≤ 25%, and good respiratory drive. In all cases, the extubation maneuver was performed by maintaining the NIRS sensor in place, and aspiration of secretions from the endotracheal tube was allowed at the discretion of the treating physician. Following extubation, CPAP or BiPAP was used as non-invasive ventilatory support based on the discretion of the treating physician. All patients underwent NIRS monitoring using the MASIMO ROOT system (Masimo Corporation, Irvine, CA, USA); the MASIMO Radical 7 device was used to monitor peripheral blood oxygen saturation (SpO_2) while the MASIMO O3 sensor was used to monitor cerebral regional oxygen saturation ($rScO_2$). The MASIMO O3 sensor provides readings every two seconds. It has been approved for use in pediatric patients, and has a reported accuracy of 3% [70]. In all patients, the adhesive sensor for cerebral $rScO_2$ monitoring was attached to the left frontoparietal region and monitoring was started within the first 5 hours of life. Peripheral SpO_2 monitoring was performed in the right upper limb. For the current study, $rScO_2$ and SpO_2 data within one hour before and one

hour after the extubation were used. To minimize errors due to movement artifacts, $rScO_2$ and SpO_2 continuous readings were averaged over a 10-minute timeframe within 1 hour before and after extubation. The chosen timeframe was based on the best stability of the rScO2 data (lower standard deviation), greater availability of data, and best proximity to the extubation. Readings pertaining to the 15 minutes immediately before and after extubation were excluded from the current analysis (Figure 1). In addition to $rScO_2$ and SpO_2, post extubation change in $rScO_2$ ($\Delta rScO_2$) and SpO_2 (ΔSpO_2) were also calculated (*i.e.,* $rScO_2$ and SpO_2 after extubation minus $rScO_2$ and SpO_2 before extubation, respectively), and cFTOE was calculated using the formula: $SpO_2 - ScO_2) / SpO_2$. The cFTOE is a useful index for assessment of cerebral regional O_2 extraction and perfusion which is independent of the variations in peripheral SpO_2.

Clinical charts of all patients were reviewed and general demographics along with GA, birth weight, 1-minute and 5-minute Apgar scores, presence (and treatment) of PDA at 48–72 hours, need for inotropic therapy, ventilatory parameters before and after extubation (*i.e.,* PIP, PEEP, and FiO_2) were collected. All patients underwent brain ultrasound examination as per the institutional protocol at days 1, 2, and 3 after birth and once a week thereafter until 36 weeks of age. Furthermore, all patients underwent cerebral magnetic resonance imaging at term age with a 3 Tesla MR system using an internal protocol that includes T1, T2, and SWI (susceptibility weighted imaging) sequence, which is highly sensitive to hemosiderin deposits[71]. Presence of GMH-IVH was reported and graded according to Volpe classification[72] .

Statistical analysis: Continuous variables were expressed as average ± standard deviation (range) unless stated otherwise; categorical variables were expressed as frequency (percentage). Pre and post extubation NIRS parameters were compared using paired *t* test. Spearman's index was used for correlation analysis and Mann–Whitney U test was used for comparison between subgroups. *P* levels ≤ 0.05 were considered indicative of statistical significance. Data were analyzed using the SPSS Statistics software, version 23 (SPSS, Chicago, IL, USA) and Microsoft Office Excel 2016 Professional (Microsoft, Redmond, WA, USA).

3. Results

Out of 46 newborns who underwent NIRS monitoring at our institution during the study period, 27 patients were excluded because they were not extubated during the monitoring period and 6 patients had movement artifacts. A total of 19 patients (14 males) were included in the current study. Average GA at birth was 29.4 weeks (range 24.9–32.6) and average birth weight was 1353 g (range 680–2170). On ultrasound screening, there were 5 cases of GMH-IVH (26.3%), 2 infants with stage I hemorrhage limited to the germinal matrix (IVH I, 10.5%), and 3 infants with stage II IVH (15.8%). Minor lesions in the periventricular white matter were confirmed in all 3 patients with stage II IVH on MRI imaging performed at term corrected age; SWI sequences (SWI+PWML) were positive for the presence of hemosiderin deposits in all 3 infants. All IVH cases were confirmed on ultrasound screening prior to extubation. A significant PDA requiring treatment was observed in 6 patients (31.6%). PDA was treated with paracetamol in 3 cases, ibuprofen in 2 cases, and both drugs in 1 case; none of the patients underwent surgical treatment (Table 1).

On average, extubation was performed at 62 hours of life (range 9–120) according to a predefined set of parameters. Preextubation parameters were as follows: average PIP 16.6 cm H_2O (range 14–21), average PEEP 4.7 cm H_2O (range 4–5.6), and average FiO_2 22% (range 21–25). Following extubation, all patients received CPAP ventilation (in 4 cases with BiLevel option) with an average PEEP of 5.4 cm H_2O (range 4–5.6) and average FiO_2 of 24% (range 21–40). There was only one case of failed extubation in our cohort (Table 1). NIRS monitoring data are summarized in Table 2. Average preextubation regional cerebral O_2 saturation was 72.9% (range 61.2–82.2) and did not change significantly after extubation (average 73.7%, range 56.5–85.3, $p = 0.536$). Likewise, there was no significant change in cerebral fractional tissue oxygen extraction index (cFTOE) after extubation (Δ 0.003, range −0.120–0.097, $p = 0.816$).

No significant change was noted in rScO2 or cFTOE index after extubation. Correlation analysis revealed a significant correlation of GA ($\rho = -0.473$, $p = 0.041$), GMH-IVH status ($\rho = 0.458$, $p = 0.048$), and preextubation PIP ($\rho = 0.470$, $p = 0.042$) with Δ cFTOE (Table 3). Likewise, we observed a significant correlation of Δ regional cerebral O_2 saturation ($rScO_2$) with GA ($\rho = 0.516$, $p = 0.024$) and IVH status ($\rho = -0.458$, $p = 0.048$). Owing to the observed significant correlations, a subgroup analysis was performed (Table 4). Patients were divided into two groups according to their GA ($\leq$28 weeks, group 1; >28 weeks, group 2) and their IVH status (IVH, group 1; no IVH, group 2). A negative Δ $rScO_2$ was observed in newborns with smaller GA compared with older infants (-4.6 ± 3.4 *vs* 2.2 ± 4.7, $p = 0.017$), although no significant difference was noted in terms of Δ cFTOE between the two groups. On the other hand, infants with IVH showed a larger increase in Δ cFTOE after extubation compared with infants without IVH (0.040 ± 0.035 *vs* -0.010 ± 0.055, $p = 0.036$).

4. Discussion

Transition from invasive mechanical ventilation to non-invasive ventilatory support is a critical event in the life of preterm infants. Early extubation or extubation failure exposes preterm neonates to the risk of apnea, hypercapnia, and need for reintubation. These factors can lead to acute fluctuations in cerebral perfusion and increase the risk of IVH [4 44]. On the other hand, prolonged or excessive mechanical ventilation can lead to hypocapnia and vasoconstriction leading to cerebral hypoperfusion and inflammation of white matter and increased risk of periventricular leukomalacia (PVL) and impaired brain development [73 74]. Several guidelines and clinical criteria have been developed to help clinicians decide on the correct timing of extubation which are typically exclusively based on the analysis of respiratory difficulties. Nevertheless, the decision-making is often challenging and it is a matter of intense debate among neonatologists.

In our study, no significant changes in rScO2 and cFTOE were found after extubation when looking at the whole population and peripheral SpO_2 levels remained substantially stable (i.e., between 91% and 95%) throughout the study period, demonstrating that the extubation maneuver was well tolerated [75]. There was no post extubation brain bleeding event and we recorded only one case of failed extubation which had no clinical consequences for the patient. No correlation was detected between extubation timing and ΔrScO2 or ΔcFTOE, even in the setting of early extubation. Nevertheless, in patients with GA < 28 weeks, extubation was associated with a significant decrease in regional brain SaO_2 compared to infants with GA ≥ 28 weeks ($\Delta rScO_2$ −4.6 ± 3.4 *vs* 2.2 ± 4.7, $p = 0.017$). However, there was no significant difference between the two groups with respect to cFTOE index. Decrease in rScO2 in extremely preterm infants can be explained by impaired cerebral autoregulation in these patients. Wong *et al.* showed how tissue oxygenation index and mean arterial blood pressure have high correlation (as a sign of lack autoregulation) in patients with lower GA [40]. Furthermore, Roche-Labarbe *et al.* also observed lower levels of cerebral oxygenation during the first 7 weeks of life of infants with GA < 31 weeks using frequency domain NIRS monitoring and the same authors also reported lower blood flow index in infants with GA between 24 and 27 weeks [76]. It is unlikely that this may be due to an increase of cerebral metabolism, as brain metabolism has been shown to increase with GA [57].

On the other hand, newborns with GMH-IVH showed a significant change in the cFTOE index following extubation (ΔcFTOE 0.040 ± 0.035 *vs* -0.010 ± 0.055, $p = 0.036$). Increase in the cFTOE index can be considered as a sign of decreased brain perfusion [13]. STROKE 2010 demonstrated that preterm infants with GMH-IVH or PVHI had lower rScO2 and higher cFTOE during the first 2 weeks after birth in comparison to infants without GMH-IVH. Lower rScO2 and higher FTOE occurred irrespective of the grade of GMH-IVH [26]. This was confirmed by Lin P-Y *et al.* who focused on low-grade GMH-IVH, and by Vesoulis ZA *et al* more recently [58 55]. Because FTOE reflects the balance between cerebral oxygen supply and cerebral oxygen consumption, increased FTOE can be explained either by reduced oxygen supply or increased oxygen consumption. A lower oxygen supply may result from lower CBF[76]. Our study highlighted worsening of the cFTOE index following extubation, which is a potential sign of further impaired cerebral blood flow autoregulation in these patients [12 27 77]. NIRS evaluates the oxygenation of most superficial cerebral tissue (approximately 2 cm of depth from the skin) [7 78]. GMH-IVH bleeding is located in the deep regions of the brain; therefore, this correlation suggests an influence on oxygenation and perfusion of more superficial areas of the brain, as previously demonstrated with MRI techniques by our group[7]. Cerebral cortex and subcortical areas (*e.g.*, subplate neurons) are very important for cerebral connectivity and neuroplasticity [79 80 81]. This further effect on the frontal areas following extubation in babies already having GMH-IVH may have greater adverse effect on the development of local neural circuitry. In addition, if a similar effect is likely to happen also in the posterior part of the brain, where brain maturation is known to be more advanced compared to the

frontal part,[82 83] impaired development of the visual cortex may also be postulated, although NIRS is unlikely to allow assessment of the posterior part of the brain for technical reasons. Vasospasm secondary to the increase in locally produced pro-inflammatory cytokines has been cited as the underlying mechanism for cerebral cortex hypoperfusion associated with GMH-IVH[84]. This could be part of a complex pathophysiological pattern that includes other pathogenic noxae such as increase in pro-inflammatory factors and reduced cell proliferation of the germinative matrix [85 86]. This may also help explain why even low-grade bleeding is associated with impaired neurological outcomes[61] and impaired periventricular white matter maturation in preterm infants[60 87 88]. Furthermore, the positioning of the NIRS sensor in our study was over the front-parietal portions of the brain that are known to exhibit delayed maturation compared to posterior portions[89]. Reduction in cerebral blood flow in these more immature areas could have a greater impact on brain maturation. At least, in our population, 3 out of the 5 patients with GMH-IVH also had SWI+PWML. This association has been previously described in literature[90] and may be correlated with altered venous blood flow and perfusion in these patients.

Some limitations of our study should be considered. The relatively small sample size may affect the generalizability of our results, in particular for subgroup analysis, where only a limited number of patients had GMH-IVH and low GA. Although $rScO_2$ data are known to be affected by blood pressure variations, it is worth noting that no inotropes were used in our patients and blood pressure values were stable throughout the study period. Finally, although we detected significant changes in cFTOE index after extubation, our monitoring data were limited to few minutes after extubation.

In conclusion, our study shows that NIRS monitoring can help detect subclinical cerebral hypoperfusion events in preterm infants. In our cohort, extubation was not related with significant cerebral blood flow fluctuation, even in the setting of early extubation. A significantly increased cerebral tissue extraction fraction of oxygen due to reduction of brain perfusion was observed following extubation in patients with GMH-IVH. This is an important finding as it can aggravate brain hypoperfusion following GMH-IVH. Furthermore, without NIRS monitoring, these hypoperfusion events would have been completely undetected due to the stability of the other parameters. These findings suggest the need for a more cautious approach when mechanically ventilated newborns with GMH-IVH are considered for extubation due to changes in ventilatory strategies or improvements in respiratory conditions. Larger studies are required to confirm these findings.

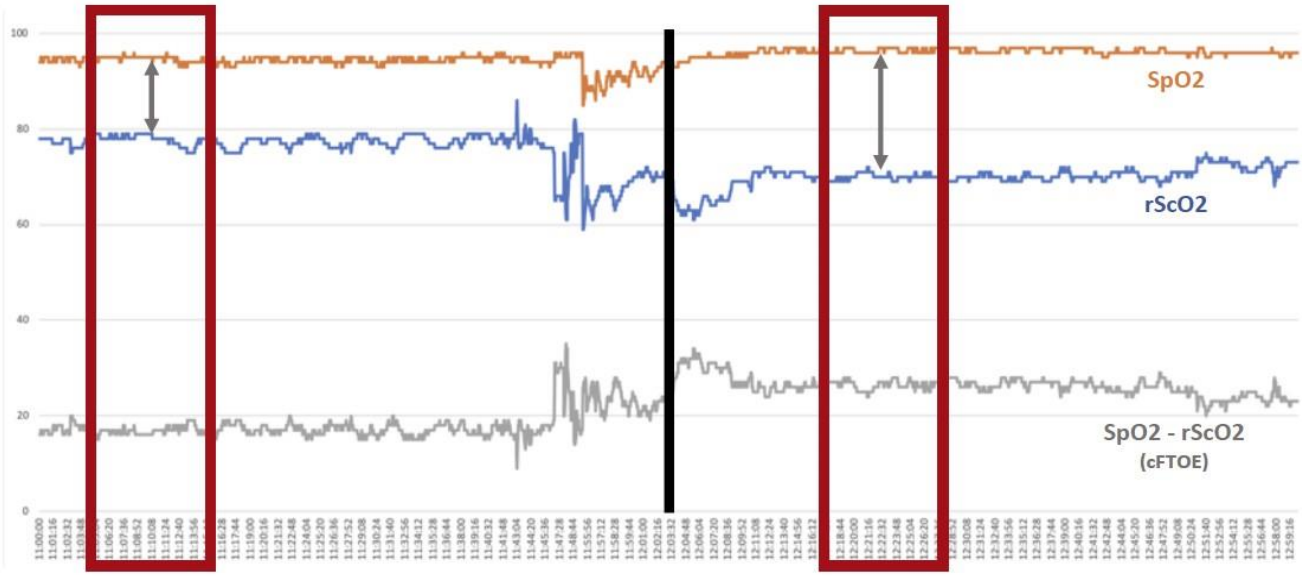

Figure 2. Red squares show the time frame selected for the analysis. The black line represents the extubation time.

Table 1. Demographic and baseline characteristics of the study population

N	19
Sex	14 M, 5 F
Gestational age (wks)	29.4 ± 2.4 (24.9 – 32.6)
Birth weight (g)	1352.9 ± 472.0 (680.0 – 2170.0)
Apgar score 1 min	5.8 ± 1.9 (1 – 9)
Apgar score 5 min	7.3 ± 1.1 (5 – 9)
IVH/GMH	5 (26.3%)
IVG > 1 (%)	3 (15.8%)
GMH (%)	2 (10.5%)
No. of significant PDA on extubation (%)	5 (26.3%)
No. of treated PDA (%)	6 (31.6%)
Treatment with inotropes (%)	0 (0.0%)
ETT removal timing (hours)	62.5 ± 37.4 (9.0 – 120.0)
Pre ETT removal	
PIP	16.6 ± 1.6 (14.0 – 21.0)
PEEP	4.8 ± 0.5 (4.0 – 5.6)
FiO_2	0.22 ± 0.15 (0.21 – 0.25)
Post ETT removal	
PEEP	5.4 ± 0.6 (4.5 – 6.5)
FiO_2	0.24 ± 0.05 (0.21 – 0.40)
Failed ETT removal	1 (5.3%)

Data are expressed as average ± standard deviation (range) unless stated otherwise; wks, weeks; g, grams; ETT, endotracheal tube; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; FiO2, fraction of inspired oxygen;

Table 2. NIRS data for the whole study population

	Before ETT removal	After ETT removal	Δ	*p**
$rScO_2$ (%)	72.9 ± 5.4 (61.2 – 82.2)	73.7 ± 7.6 (56.5 – 85.3)	0.7 ± 5.2 (-7.8 – 11.9)	0.536
SpO_2 (%)	93.6 ± 2.8 (88.3 – 97.7)	94.2 ± 3.1 (88.5 – 99.2)	0.6 ± 3.6 (-7.0 – 8.1)	0.507
cFTOE	0.216 ± 0.053 (0.140 – 0.358)	0.219 ± 0.070 (0.097 – 0.403)	0.003 ± 0.054 (-0.120 – 0.097)	0.816

Data are expressed as average ± standard deviation (range) unless stated otherwise; $rScO_2$, regional cerebral oxygen saturation; SpO_2, peripheral oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; ETT, endotracheal tube; Δ, after ETT removal – before ETT removal; * *p* values from paired-samples *t* test

Table 3. Correlation analysis

	Δ cFTOE		Δ $rScO_2$	
	ρ	*p*	ρ	*p*
Gestational age	**-0.473**	**0.041**	**0.516**	**0.024**
Birth weight	-0.331	0.166	0.266	0.271
Apgar 1 min	-0.049	0.843	0.308	0.199
Apgar 5 min	0.403	0.087	-0.078	0.750
IVH / GMH	**0.458**	**0.048**	**-0.458**	**0.048**
PDA on extubation	0.262	0.279	-0.371	0.118
Treated PDA	0.269	0.266	-0.207	0.396
Extubation timing	0.283	0.241	-0.147	0.549
Pre-extubation				
PIP	**0.470**	**0.042**	-0.150	0.540
PEEP	-0.117	0.633	0.077	0.753
FiO_2	0.211	0.386	-0.369	0.120
Post-extubation				
PEEP	0.155	0.526	-0.261	0.280
FiO_2	0.255	0.292	-0.372	0.117
Ventilatory support	0.377	0.111	-0.424	0.070

ρ = Spearmann's rank correlation coefficient;

Table 4a. Subgroup analysis

	GA < 28 weeks (n = 4)			GA ≥ 28 weeks (n = 15)			
	Pre	Post	Δ	Pre	Post	Δ	*p*
$rScO_2$ (%)	72.4 ± 3.8	67.8 ± 2.5	-4.6 ± 3.4	73.0 ± 5.9	75.2 ± 7.8	2.2 ± 4.7	**0.017**
SpO_2 (%)	93.1 ± 3.6	90.9 ± 1.4	-2.2 ± 4.8	93.8 ± 2.7	95.1 ± 2.8	1.3 ± 3.0	0.245
cFTOE	0.208 ± 0.048	0.254 ± 0.289	0.046 ± 0.037	0.218 ± 0.056	0.210 ± 0.075	-0.008 ± 0.053	0.051
	IVH / GMH (n = 5)			No IVH /GMH (n = 14)			
	Pre	Post	Δ	Pre	Post	Δ	*p*
$rScO_2$ (%)	69.7 ± 6.1	66.7 ± 6.1	-3.0 ± 4.4	74.1 ± 4.8	76.2 ± 6.6	2.1 ± 5.0	0.066
SpO_2 (%)	93.2 ± 3.2	94.4 ± 3.8	1.1 ± 5.4	93.8 ± 2.8	94.1 ± 2.9	0.4 ± 3.0	0.787
cFTOE	0.252 ± 0.065	0.292 ± 0.062	0.040 ± 0.035	0.203 ± 0.044	0.193 ± 0.053	-0.010 ± 0.055	**0.036**

Data are expressed as average ± standard deviation unless stated otherwise; Pre, before endotracheal tube removal; Post, after endotracheal tube removal; $rScO_2$, regional cerebral oxygen saturation; SpO_2, peripheral oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; GA, gestational age; IVH / GMH, intraventricular hemorrhage;

Table 4b. Subgroup analysis

	GA ≤ 28 weeks (n = 4)				GA > 28 weeks (n = 15)			
	Pre	Post	Δ	*p*	Pre	Post	Δ	*p*
$rScO_2$ (%)	72.4 ± 3.8	67.8 ± 2.5	-4.6 ± 3.4	0.14	73.1 ± 5.9	75.2 ± 7.9	2.2 ± 4.1	0.11
SpO_2 (%)	93.1 ± 3.6	90.9 ± 1.4	-2.2 ± 4.8	0.27	93.8 ± 2.7	95.1 ± 2.8	1.3 ± 3.1	0.19
cFTOE	0.208 ± 0.048	0.254 ± 0.029	0.046 ± 0.037	0.07	0.218 ± 0.056	0.210 ± 0.075	-0.008 ± 0.053	0.57
	IVH / GMH (n = 5)				No IVH /GMH (n = 14)			
	Pre	Post	Δ	*p*	Pre	Post	Δ	*p*
$rScO_2$ (%)	69.7 ± 6.1	66.7 ± 6.1	-3.0 ± 4.4	0.22	74.1 ± 4.8	76.2 ± 6.6	2.1 ± 5.0	0.16
SpO_2 (%)	93.2 ± 3.2	94.4 ± 3.8	1.1 ± 5.4	0.50	93.8 ± 2.8	94.1 ± 2.9	0.4 ± 3.0	0.58
cFTOE	0.252 ± 0.065	0.292 ± 0.062	0.040 ± 0.035	**0.04**	0.203 ± 0.044	0.193 ± 0.053	-0.010 ± 0.055	0.78

Data are expressed as average ± standard deviation unless stated otherwise; Pre, before endotracheal tube removal; Post, after endotracheal tube removal; $rScO_2$, regional cerebral oxygen saturation; SpO_2, peripheral oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; GA, gestational age; IVH / GMH, intraventricular hemorrhage;

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