



REVIEW ARTICLE

Monitoring cerebral oxygenation of the immature brain: a neuroprotective strategy?

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Monitoring of cerebral oxygenation (rScO₂) with near-infrared spectroscopy (NIRS) is a feasible noninvasive bedside technique in the NICU. This review discusses the possible neuroprotective role of “pattern recognition” of NIRS-derived rScO₂ in preterm neonates with regard to the prevention of severe intraventricular hemorrhage and hypoxia/hyperoxia-related white matter injury. This neuroprotective role of rScO₂ monitoring is discussed as a modality to aid in the early detection of cerebral oxygenation conditions predisposing to these complications. Practical guidelines are provided concerning management of abnormal rScO₂ patterns as well as a brief discussion concerning the need for international consensus and the legal aspects associated with the introduction of a new NICU bedside monitoring strategy.

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INTRODUCTION

Near-infrared spectroscopy (NIRS) offers the ability to noninvasively monitor alterations in oxygenation, oxygen extraction, and perfusion of the immature brain.^{1–3} A recent study showed that NIRS-derived regional cerebral saturation (rScO₂; %), which is a mixture of venous (~75%), capillary (~5%), and arterial saturation (~20%), correlates well with magnetic resonance imaging (MRI)-determined cerebral oxygenation.⁴ Further, combining NIRS-monitored rScO₂ with simultaneous mean arterial pressure can be used as a clinical tool to assess and trend cerebral autoregulation in both premature and term neonates.^{5,6} A recent multicenter interventional study, the SafeboosC Study, demonstrated that cerebral oxygenation was quite stable and mostly within the expected reference ranges (55–85%) in 166 extremely preterm neonates during the first 72 h of postnatal life when rScO₂ was monitored.^{7,8} Moreover, decreased hypoxia burden was associated with a lower incidence of severe intraventricular hemorrhage in the rScO₂-monitored cohort.⁹ This result was consistent with previous data demonstrating an association between both cerebral hyperoxia and hypoxia with adverse long-term neurodevelopmental outcome.¹⁰

Nonetheless, though commonly encountered in the research setting, the clinical application of cerebral oxygenation monitoring in the neonatal intensive care unit (NICU) remains highly limited. Indeed, NIRS-based cerebral oxygenation monitoring remains at best a “trend monitoring” technique, based on variable precision and data averaging techniques across a range of studies.^{11–14} Moreover, other studies have shown differences in rScO₂ based on utilizing different NIRS devices and sensors, most likely due to variable algorithms being employed.^{12,15} Finally, uncertainty beneath which thresholds tissue oxygen utilization becomes delivery-dependent has limited its widespread adoption.¹² However, from a “trend monitoring” perspective, NIRS-derived cerebral oxygenation may provide valuable bedside information with

implications for clinical management. If merely used for “pattern recognition”, such monitoring may be considered a potential early warning sign prompting further evaluation, especially if the values of rScO₂ remain outside the published reference ranges.^{8,15}

In this review, we will focus on the potential utility of continuous NIRS-based cerebral tissue oxygenation monitoring as a component of a neuroprotective strategy in premature neonates (Fig. 1). A more detailed explanation of the NIRS monitoring technique, including its validation and general reference ranges, is beyond the focus of this review, though it is discussed in numerous other articles.^{1,2,8,11,12}

CEREBRAL OXYGENATION MONITORING AND THE PRETERM NEONATE

Periventricular–intraventricular hemorrhage (PIVH) and diffuse white matter injury (WMI) are important contributors to adverse neurodevelopmental outcomes among preterm neonates.^{16–18} The neuroprotective role of NIRS-based cerebral oxygenation monitoring via general “pattern recognition” techniques are detailed below. In the present review, we discuss strategies to aid in the prevention of severe PIVH, followed by an overview of techniques to potentially reduce the burden of cerebral hypoxia/hyperoxia with the goal of reducing WMI in the preterm population.

PREVENTION OF SEVERE INTRAVENTRICULAR HEMORRHAGE

The pathogenesis of PIVH, although multifactorial,^{18,19} is firmly linked to immaturity of the preterm infant and more specifically to vascular immaturity within the germinal matrix, the usual origin of PIVH.²⁰ Immaturity of several organ systems, in particular the lungs, with or without inflammation, results in neonatal respiratory distress syndrome (RDS), which facilitates important clinical

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Fig. 1 Representative fixation of near Infrared sensor in a preterm infant at the parieto-frontal position of the skull (courtesy Liesbeth Thewissen, UZ Leuven)

conditions predisposing for extension of PIVH. The most important etiologic factors for PIVH in this respect are hypercapnia, lack of cerebral autoregulation, and apparent hypotension often resulting in anti-hypotensive treatment. Hypercapnia-induced cerebral hyperperfusion,^{18,21} a pressure-passive perfusion of the brain,²² and hypotension-induced use of inotropic agents²¹ are all related to the occurrence and extension of PIVH. Monitoring rScO₂ patterns can aid clinicians in identifying and potentially correcting these conditions during earlier stages.

Hypercapnia-induced cerebral hyperperfusion

Ongoing assessment of rScO₂ patterns has been shown to provide information on hypercapnia-induced cerebral hyperperfusion. Awareness of abnormal rScO₂ trending during hypercapnia, demonstrated in Fig. 2a, may result in earlier detection and correction of severe hypercapnia in mechanically ventilated infants with consequent normalization of brain perfusion and oxygenation. Since acute increases in PaCO₂, even within normal limits, can result in increased cerebral blood flow,²³ employing tight PaCO₂ limits during the first 72 postnatal hours could conceivably improve the stability of cerebral perfusion as indicated by a stable rScO₂ within normal limits.

Pressure-passive brain perfusion

Impaired cerebral autoregulation can be recognized in rScO₂ patterns which passively follow the mean arterial blood pressure,^{5,6} as depicted in Fig. 2b. Consequently, this monitoring technique may aid in identifying neonates particularly sensitive to handling who may benefit from sedation to minimize swings in cerebral perfusion in the context of impaired cerebral autoregulation. In addition, among hypotensive premature neonates, examining the relationship between blood pressure and rScO₂ may allow clinicians to better select those patients who would most benefit from inotropic support rather than relying on mean arterial blood pressure alone (see also below).

Hypotension-induced use of inotropic agents

With regard to blood pressure management, a prior study by the Utrecht group suggested that neonatal hypotension, defined as a mean arterial blood pressure lower than the gestational age at birth, is unreliable and possibly associated with overtreatment.²⁴ Moreover, Alderliesten et al.²¹ reported that inotropes, such as dopamine, can induce cerebral hyperperfusion and loss of cerebral autoregulation among premature neonates. Figure 2c represents a typical example. They further reported that elevated rScO₂ values, with resultant cerebral hyperperfusion and loss of cerebral autoregulation, preceded the occurrence and in particular

the extension of already-existing PIVHs.²¹ The same group reported that hypotension alone, as defined using the above gestational age criteria, was neither related to low rScO₂ values nor to impaired neurodevelopmental outcome at 2 years of age.²⁵ Currently, the TOHOP study, a single-center, randomized study in the Utrecht NICU is assessing “permissive” hypotension in the study group based on rScO₂ values remaining within the normal limits (55–85% as investigated in a prior prospective study⁸ in addition to normal blood gases, urine output, and capillary refill).

Taken together, these observations may result in improved personalization of critical care such that more appropriate, and potentially neuroprotective, strategies may be employed where needed. Cerebral oxygenation monitoring may set the stage for more timely and patient-specific management, with potential reduction in PIVH and ultimately improved neurodevelopmental outcomes.

Table 1 summarizes the most important conditions related to elevated rScO₂ values.

PREVENTION OF WMI

WMI occurs in up to 50% of extremely and very preterm neonates according to several recent MRI studies,^{26–28} with substantial implications for neurodevelopmental outcome (25–50%) and cerebral palsy (5–10%).²⁹ Although antenatal WMI has been well described due to maternal/fetal infection or fetal hypoxia^{18,30} and is beyond the focus of this review, postnatal cerebral hypoxia–ischemia (HI) is also a potentially important etiologic factor for WMI. The conditions associated with cerebral hypoperfusion and subsequent HI include hypocapnia;^{31,32} hemodynamically significant patent ductus arteriosus (hsPDA);^{33,34} severe anemia and/or blood loss;^{35–37} hypoglycemia;³⁸ and progressive posthemorrhagic ventricular dilatation (PHVD).^{35,39} Monitoring the rScO₂ patterns can potentially aid clinicians in identifying and correcting these conditions at an early stage, with the goal of preventing or attenuating HI and ultimately improving outcomes.

Hypocapnia

Conversely to hypercapnia-induced cerebral hyperperfusion, acute hypocapnia can cause sudden decreases in cerebral perfusion.²³ Special attention to this phenomenon is particularly important in mechanically ventilated infants should overventilation occur. Of note, PaCO₂ values below 30 mmHg have been associated with significant effects on cerebral perfusion⁴⁰ (Fig. 3a). In a cerebral monitoring paradigm, decreasing rScO₂ to abnormally low values in a ventilated neonate could serve as an early warning sign for overventilation, prompting assessment of PaCO₂ as a potential etiology.

Hemodynamically significant PDA

Although management of hsPDA remains a controversial issue,^{41,42} cerebral oxygenation can be impaired by an hsPDA, with potentially severe ranging rScO₂ values below 40–45% (Fig. 3b).³⁴ Furthermore, prolonged duration (>30–60 min) of cerebral hypoxia at these low values has been associated with cerebral injury and/or impaired cerebral metabolism in several experimental and clinical studies.^{43–46} Previous studies in extremely preterm neonates have demonstrated a negative impact of hsPDA on cerebellar growth.^{47,48} In a large cohort of preterm infants with hsPDA, we previously reported that a longstanding open ductus can affect cerebellar growth, using volume-based measurements. This growth impairment was independently and directly related to cerebral tissue oxygenation.³⁴ Among premature neonates with a known hsPDA, it thus follows that rScO₂ pattern monitoring, especially when demonstrating severe-range cerebral hypoxia, may impact treatment decisions regarding the need for PDA closure.³⁴

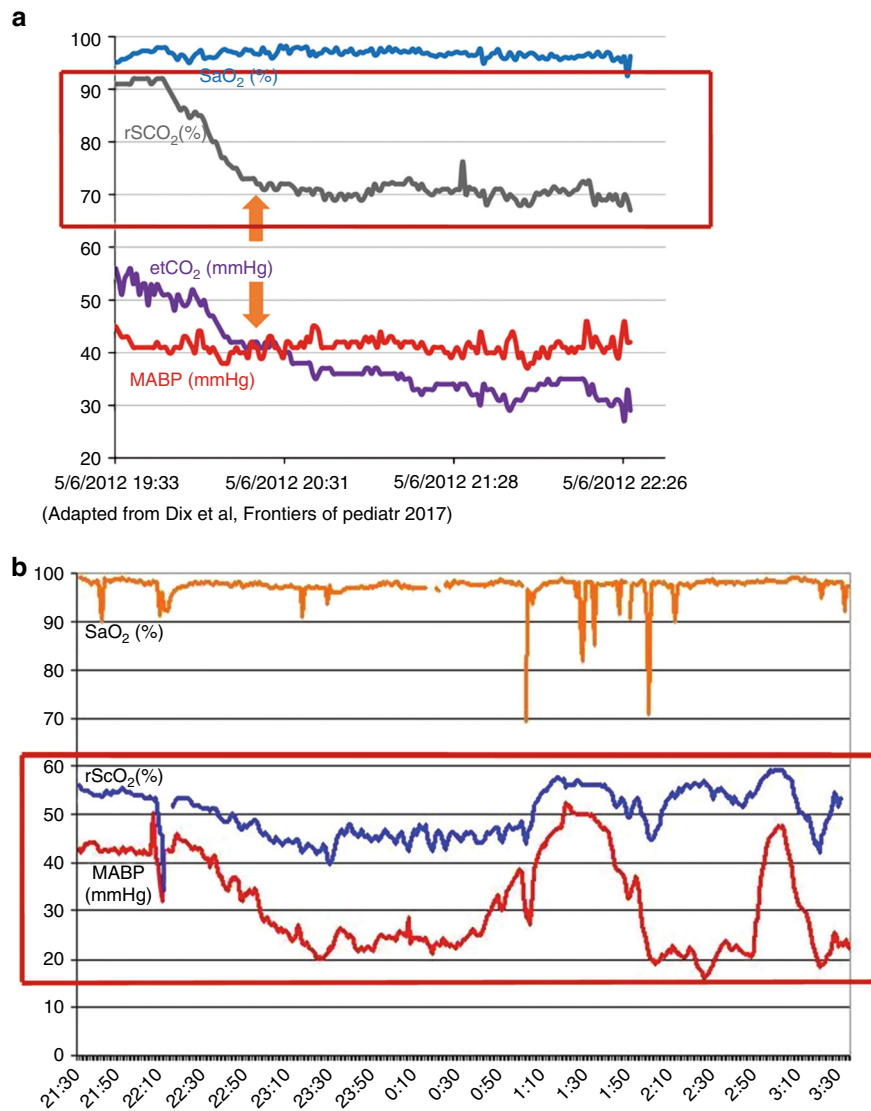


Fig. 2 **a** The patterns of rScO₂ (in red box) and end-tidal (et) CO₂ (purple: as a surrogate for arterial PaCO₂) both decreasing from supranormal values, indicating hyperoxygenation/overperfusion (rScO₂: 91%) and hypercapnia (etCO₂: 58 mmHg), respectively, to normal values (72% and 41 mmHg, respectively; orange arrows) after ventilator adjustment. Note the normal arterial pressure (MABP) and that a normal arterial oxygen saturation (SaO₂) is not indicative of normal cerebral oxygenation. Adapted from Dix et al.² **b** The red box includes the pattern of cerebral oxygenation (blue) as represented by rScO₂, which passively follows mean arterial blood pressure (MABP; red) in a girl born at 26 0/7 weeks on postnatal day 1, strongly suggesting lack of cerebral autoregulation.

Anemia

Numerous reports have demonstrated a negative association between anemia and cerebral oxygenation,^{35,36} and especially at hemoglobin values below 6 mmol/L.³⁷ These same studies have additionally demonstrated improved cerebral and peripheral tissue oxygenation following packed red blood cell transfusion (Fig. 3c).^{49,50} Thus, proactive rScO₂ monitoring may aid clinicians in determining the transfusion needs among premature neonates with already marginal hematocrits.

Hypoglycemia

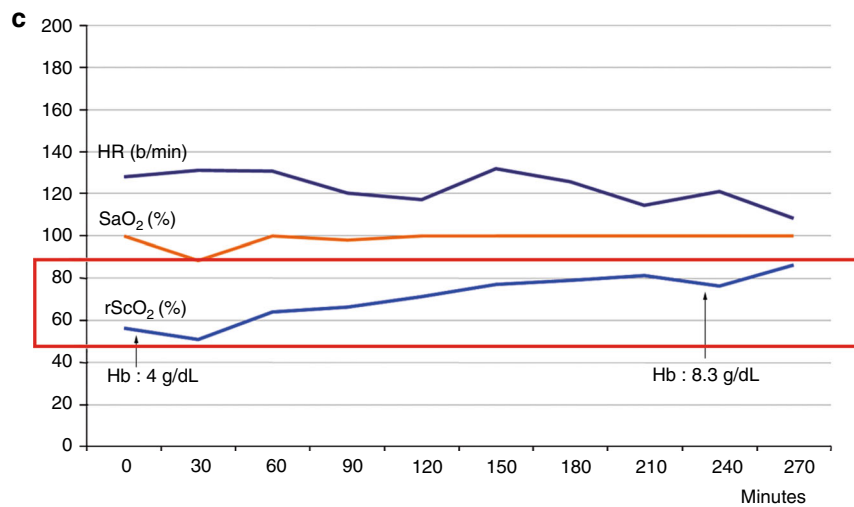
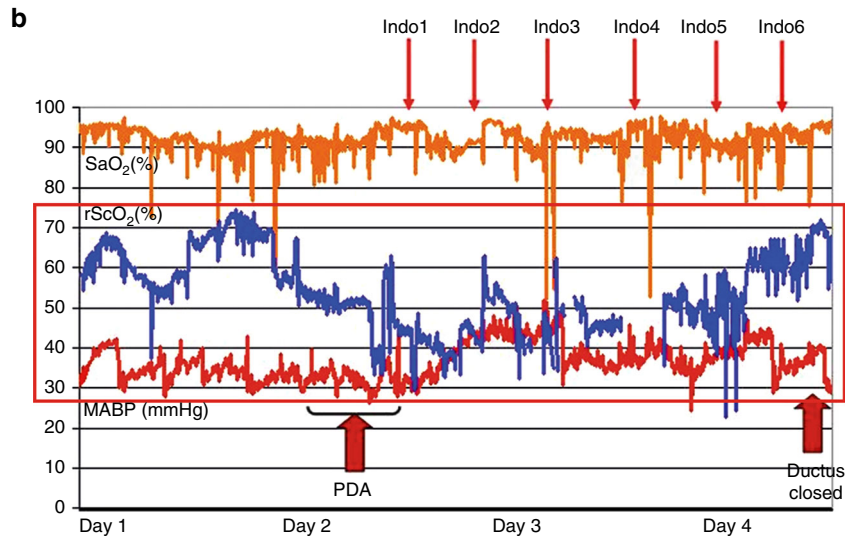
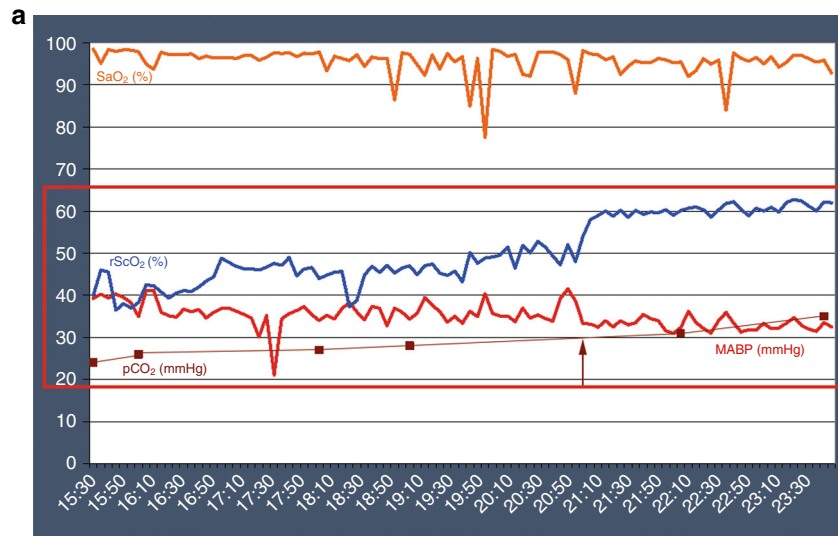
During hypoglycemia, cerebral oxygenation increases, an insidious sign potentially indicative of a shortage in glucose and/or other substrates for cerebral metabolism and hence a redistribution of blood flow to the brain to enhance oxygen delivery.³⁸ Whether rScO₂ pattern monitoring can aid in hypoglycemia-related clinical management is yet to be elucidated, though the noninvasive nature of cerebral monitoring may provide value-addition at minimal risk.

PHVD

Finally, when progressive PHVD is diagnosed, increasing pressure exerted on the cerebral parenchyma by the expanding lateral ventricles can negatively impact cerebral tissue perfusion.^{39,51} Although not much is known about the consequences on tissue oxygenation, a recent study by Kochan et al.³⁹ demonstrated rScO₂ often below 40%, values which have been associated with cerebral impairment.^{43–46}

APPLYING RSCO₂ "PATTERN RECOGNITION" IN CLINICAL PRACTICE?

As discussed above, observation of cerebral oxygenation patterns using NIRS-derived rScO₂ and timely recognition of suboptimal patterns can potentially aid clinicians in avoiding various neonatal conditions associated with untoward cerebral consequences. Nurses, physician assistants, residents, and medical staff must be instructed according to practical guidelines concerning the interpretation of rScO₂ patterns. Table 1 lists the most



frequently occurring conditions, derived from the SafeboosC study,⁵² which may impact cerebral oxygenation and perfusion patterns. Applying rScO₂ monitoring to clinical practice is predominantly a matter of discerning which condition(s) is/are

most likely contributing to the changes in cerebral oxygen patterns for a given neonate.

In the University Medical Center Utrecht NICU, instruction sessions on physiologic basics and clinical use of cerebral NIRS are

Fig. 3 **a** The patterns of arterial saturation (SaO₂; orange), and rScO₂ (blue) and mean arterial blood pressure (MABP; red) of an extremely preterm infant on postnatal day 1. The initial rScO₂ values were very low (red box). These low values seemed to be associated with PaCO₂ values below 30 mmHg (brown squares; starting at 24 mmHg, see also brown arrows). SaO₂ and MABPs values were always normal. When PaCO₂ values increased above values of 30 mmHg the rScO₂ increased and eventually normalized. **b** The patterns of rScO₂ (blue) and mean arterial blood pressure (MABP; red) of a very preterm girl, starting on postnatal day 1, was especially marked by a steep decrease in cerebral oxygenation (rScO₂; red box) to very low values (<40%). Echocardiographic investigation early on postnatal day 2 revealed a hemodynamically significant ductus arteriosus. Subsequent ductal closure with indomethacin (2 courses) was followed by normalization of cerebral oxygenation. **c** The patterns of heart rate (HR), arterial saturation (SaO₂) and rScO₂ (red box) in a preterm neonate with severe anemia. The rather low rScO₂ recovered following packed red blood cell transfusion (courtesy Prof. Gunnar Nauelaers, UZ Leuven).

Table 1. Summary of the most important conditions related to decreased rScO₂ values

Important factors influencing perfusion of the immature brain	
Increase rScO ₂	Decrease rScO ₂
Hypercapnia ^{1,23}	Hypocapnia ^{1,23}
Lack of cerebral autoregulation ^{5,6,21}	Hemodynamically significant PDA ^{33,34}
Inotropic therapy for hypotension ^{24,25}	Severe anemia ³⁵⁻³⁷
Inappropriate FiO ₂ ⁷	Hypoglycemia ³⁸
	Posthemorrhagic ventricular dilatation ^{39,51}
	Hypoxia
	Hypotension ^{24,25}
	Lack of cerebral autoregulation ^{5,6,21}

provided on a regular basis. During these sessions, “pattern recognition” with regard to cerebral oxygenation and/or extraction are discussed in interactive sessions. Interpretation of these patterns and possible interventional actions based on these interpretations are embedded within practical guidelines (see summary in Table 1) and reasonably implemented in the daily care of very and extremely preterm neonates. An e-learning program is available for the nurses and medical staff. All infants born at less than 30 weeks’ gestational age undergo rScO₂ monitoring from NICU admission to 72 h of age, assuming this to be the most vulnerable period. Following 72 postnatal hours, cerebral oxygenation monitoring is continued in unstable infants remaining on the ventilator and/or those with an hsPDA. In any neonate, rScO₂ monitoring may be restarted as needed, such as in the case of progressive PHVD. In all neonates, rScO₂ monitoring is depicted in real-time at the bedside and is collected in the electronic medical record. Concomitant conventional monitoring is displayed alongside rScO₂ data (e.g., mean arterial pressure). Additionally, offline analysis of rScO₂ and conventional monitoring is possible using an in-house developed database (Signalbase™).

ISSUES TO BE SOLVED

Establishing large-scale clinical application of NIRS-based cerebral oxygenation monitoring in the NICU requires international consensus among the neonatal community. Normative values and expected quiescent variability remain elusive data, which are critical to understanding cerebral oxygen utilization patterns among preterm neonates. Moreover, how these “normal” patterns are expected to change in response to single or multiple neonatal conditions remains an area of significant ongoing inquiry and controversy. In addition, though this review focuses solely on pattern recognition with regard to cerebral oxygenation monitoring, a growing body of work incorporates comparisons between cerebral and peripheral oxygenation measures.⁵³ Ongoing research is required to determine how simultaneous multiregion monitoring may further clarify individual patients’ changes in

clinical status. As we have described rScO₂ effects related to individual conditions above, an individual patient’s physiology requires individual management, and certainly no set of cerebral oxygenation “rules” may apply to all neonates.

LEGAL IMPLICATIONS

Also important for wide-scale utilization of rScO₂ monitoring are the challenges and legal implications behind introducing new monitoring techniques. In a recent comprehensive review, Andersen et al. described the potential use of NIRS-derived monitoring of oxygenation adequacy as a factor in neonatal management.⁵⁴ While this review focuses on cerebral oxygenation, peripheral forms of tissue oxygenation monitoring are also mentioned as potential contributors to an assessment of a given neonate’s overall physiologic oxygenation status. In addition, the introduction of a new monitoring strategy as a standard of care requires an eventual diminishing of equipoise concerning effects on outcomes, along with broad acceptance among clinicians and practitioners. At present, while rScO₂ pattern monitoring shows promise for improved individualization of neonatal care and potentially earlier recognition of a variety of conditions associated with cerebral impairment, whether this monitoring ultimately impacts long-term outcomes is yet to be definitively proven.

CONCLUSION

Ongoing assessment and “pattern recognition” of NIRS-derived cerebral oxygen saturation (rScO₂) seems a relatively simple modality for potentially preventing or reducing the incidence of severe PIVH and/or WMI in very and extremely preterm neonates. International collaboration and consensus are required to increase the utilization of this potentially neuroprotective strategy.

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ADDITIONAL INFORMATION

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