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REVIEW ARTICLE

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Near-infrared spectroscopy monitoring of neonatal cerebrovascular reactivity: where are we now?

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Cerebrovascular reactivity defines the ability of the cerebral vasculature to regulate its resistance in response to both local and systemic factors to ensure an adequate cerebral blood flow to meet the metabolic demands of the brain. The increasing adoption of near-infrared spectroscopy (NIRS) for non-invasive monitoring of cerebral oxygenation and perfusion allowed investigation of the mechanisms underlying cerebrovascular reactivity in the neonatal population, confirming important associations with pathological conditions including the development of brain injury and adverse neurodevelopmental outcomes. However, the current literature on neonatal cerebrovascular reactivity is mainly still based on small, observational studies and is characterised by methodological heterogeneity; this has hindered the routine application of NIRS-based monitoring of cerebrovascular reactivity to identify infants most at risk of brain injury. This review aims (1) to provide an updated review on neonatal cerebrovascular reactivity, assessed using NIRS; (2) to identify critical points that need to be addressed with targeted research; and (3) to propose feasibility trials in order to fill the current knowledge gaps and to possibly develop a preventive or curative approach for preterm brain injury.

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IMPACT:

- NIRS monitoring has been largely applied in neonatal research to assess cerebrovascular reactivity in response to blood pressure, $PaCO_2$ and other biochemical or metabolic factors, providing novel insights into the pathophysiological mechanisms underlying cerebral blood flow regulation. Despite these insights, the current literature shows important pitfalls that would benefit to be addressed in a series of targeted trials, proposed in the present review, in order to translate the assessment of cerebrovascular reactivity into routine monitoring in neonatal clinical practice.

INTRODUCTION

The ability of the cerebral vasculature to regulate its resistance in response to both local and systemic factors is defined as cerebrovascular reactivity (CR) and is aimed at maintaining adequate cerebral blood flow (CBF) to meet cerebral metabolic demand. Neonatal CR was first studied using radioactive tracer methods and Doppler sonography. The application of non-invasive and operator-independent near-infrared spectroscopy (NIRS) technique for cerebral regional tissue oxygen saturation ($rStO_2$) monitoring in neonatal settings has shed further light on CR in several physiological and pathological conditions. Nevertheless, the methodological heterogeneity, along with the observational nature and the small sample sizes of current reports, hinders a routine application of CR monitoring for neonatal neuroprotection. On these premises, we aim to provide an updated review of NIRS-based evidence on neonatal CR and to identify critical issues and gaps that should be addressed with targeted trials to implement CR monitoring in neonatal intensive care.

PHYSIOLOGICAL MECHANISMS OF CEREBROVASCULAR REACTIVITY

Pressure-flow autoregulation

The modulation of vascular tone in relation to intraluminal pressure is a leading mechanism of CBF regulation, mediated by the mechanoreceptor properties of smooth muscle cells lining cerebral

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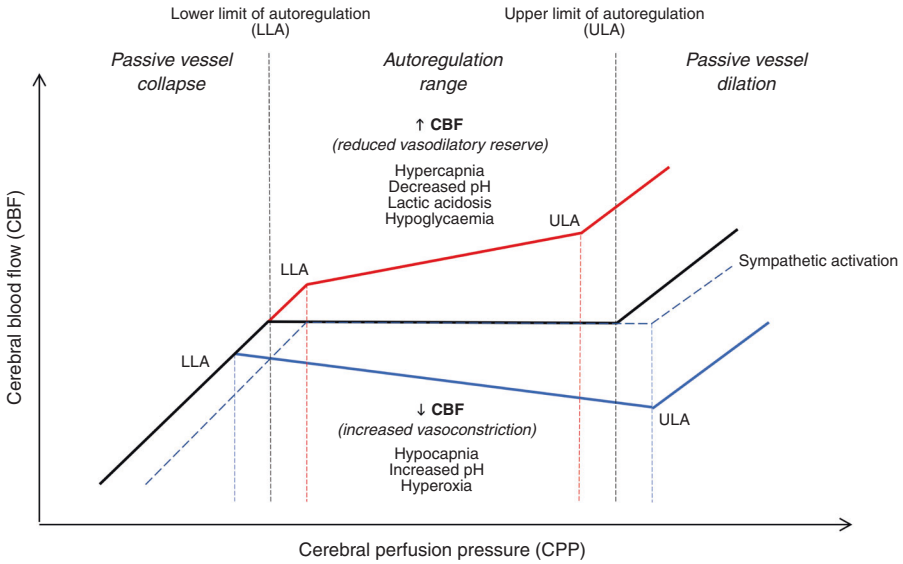

Fig. 1 Relationship between pressure-flow, metabolic and biochemical regulation of cerebral blood flow (CBF). The main determinant of cerebral perfusion pressure (CPP, shown in the *x*-axis) in the neonatal brain is arterial blood pressure. The black line indicates pressure-flow regulation under physiological homoeostatic conditions (i.e., normal pH, $PaCO_2$, PaO_2, normoglycaemia, basal autonomic status). The red line illustrates changes in CBF and in its relationship with CPP under hypercapnia and other conditions determining cerebral vasodilation, which may reduce the vasodilatory reserve and shorten the autoregulatory plateau. The blue line illustrates the changes in CBF and in its relationship with CPP under hypocapnia or associated conditions, which may widen the autoregulatory plateau. The dashed black line indicates the effect of sympathetic activation on the pressure-flow regulation curve. The dotted vertical lines indicate the upper (ULA) and lower (LLA) limits of the autoregulatory plateau in different conditions.

arteries. In response to increased intraluminal pressure, membrane depolarisation and calcium-dependent vasoconstriction occur, while the opposite happens at low intraluminal pressure, resulting in cerebral vasodilation.[1] The classic depiction of cerebral pressure-flow autoregulation is a sigmoidal curve (Fig. 1), with stable CBF over a range of cerebral perfusion pressure (CPP), of which a main determinant in neonates is arterial blood pressure (ABP). When ABP values fall below the lower limit or rise above the upper limit of autoregulatory capacity, pressure-passive circulation occurs, with potential ischaemic or haemorrhagic complications.[2] Recent evidence from adults, however, has revised this classical view by showing a much shorter plateau which still has a gentle slope, indicating some degree of pressure-passive CBF.[3,4] Notably, 'cerebral autoregulation' is often used to refer to 'cerebrovascular reactivity'. However, although the pressure-flow autoregulation of CBF is frequently involved in the interplay between CR mechanisms, the two terms are not synonymous, and their interchangeable use may contribute to the heterogeneity seen in current literature.

Biochemical factors

Partial arterial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) are potent chemo-modulators of cerebral vasculature, independent of intravascular pressure. While hypoxia and hypercapnia exert a vasodilatory effect on CBF, hyperoxia and hypocapnia lead to cerebral vasoconstriction. Vascular reactivity to PaO_2 and $PaCO_2$ is mediated by H^+/K^+ homoeostasis, secondary to changes in perivascular pH.[5–7] CR to PaO_2, $PaCO_2$ and ABP can functionally interact (Fig. 1). For example, if the vasodilator pathway has been activated during hypercapnia, the slope of the autoregulatory plateau increases, predisposing to larger CBF fluctuations even when ABP/CPP are within the normal range.[8]

Metabolic factors

Cerebral metabolic demands can influence cerebral perfusion, as supported by the evidence of CBF changes in relation to glucose availability. In preterm newborns, hypoglycaemia is associated with a significant compensatory increase in CBF;[9] following the restoration of normoglycaemia, CBF gradually decreases.[10] A recent systematic review[11] has also reported a similar negative correlation between blood glucose levels and either cerebral $rStO_2$ or haemoglobin concentration,[12–14] used as a proxy for CBF, in term and preterm neonates.

Sympathetic nervous system

The cerebral vasculature has abundant adrenergic receptors and is under precise autonomic control.[15] Sympathetic activation shifts the autoregulatory plateau towards higher CPP, thereby protecting the brain against hyperperfusion (see Fig. 1).[16] The sympathetic system appears to play a greater role in CBF regulation in the perinatal period than later in life.[17] The relative immaturity of nitric oxide (NO)-induced vasodilatory mechanisms during early development, the greater sensitivity to exogenous norepinephrine and the higher sympathetic nerve density in neonatal compared to adult pial arteries may contribute to this finding.[18]

Functional activation

The CBF response to neuronal activation is referred to as neurovascular coupling. This response is mediated by the neurovascular unit (Fig. 2), which represents an interactive network of cerebral vessels, vascular cells (pericytes, smooth muscle and endothelial cells), glia (astrocytes and microglia) and perivascular neurons. Upon neuronal activation, vasoactive substances such as prostaglandins, NO and adenosine are released from both neurons and astrocytes, leading to the modulation of vascular smooth muscle.[19] Studies using functional NIRS have provided insight into the neurovascular coupling response in newborns. In the adult brain, the classic 'positive' response is characterised by an increase in oxygenated haemoglobin (O_2Hb) and a decrease in deoxygenated haemoglobin (HHb). In neonates, however, variable cerebral haemodynamic patterns have been reported in response to neuronal activation, including a 'negative' response with local O_2Hb reduction, which may indicate that the oxygen consumption triggered by neuronal activity transiently outpaces the concomitant CBF increase.[20–24] This variability may be due to developmental changes in the

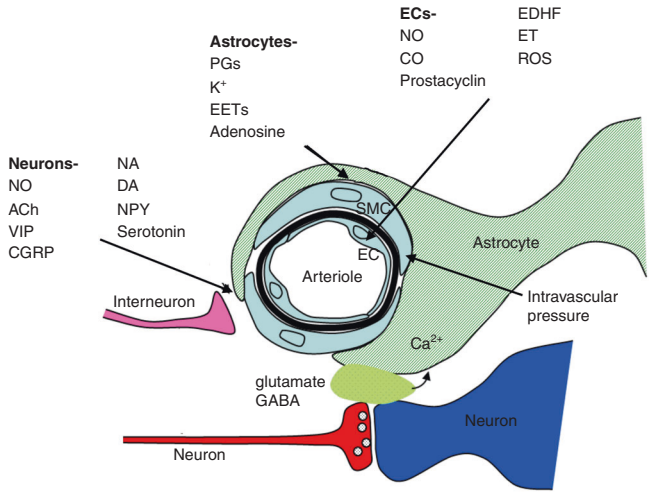

Fig. 2 Illustration of the neurovascular unit and of the complex interplay between arteriole, interneuron, astrocyte, and neuron-secreted factors on smooth muscle cells, which regulate the vascular arteriole diameter. CO carbon monoxide, SMC smooth muscle cell, EC endothelial cell, Ach acetylcholine, PGs prostaglandins, EETs epoxyeicosatrienoic acids, VIP vasoactive intestinal polypeptide, CGRP calcitonin gene-related peptide, NA noradrenaline, DA dopamine, NPY neuropeptide Y, EDHF endothelium-derived hyperpolarizing factor, ET endothelin, GABA γ-aminobutyric acid, ROS reactive oxygen species. Reproduced with permission from Brew et al.[38].

capacity of cerebral vasculature to produce functional hyperaemia in the low-density capillary bed of the neonatal brain.[25,26]

NIRS-BASED ASSESSMENT OF CEREBROVASCULAR REACTIVITY: SURROGATE SIGNALS AND NEONATAL APPLICATIONS

The assessment of CBF fluctuations in response to physiological changes or stimuli is fundamental to evaluate the integrity of CR. This assessment evaluates the relationship between the input and the output (i.e., CBF) signals,[27] and can be classified into static, which includes quantitative methods performing point measurements of CBF (e.g.,^{133}Xe clearance), or dynamic.[28,29] While in adults, transcranial Doppler sonography (TCD) can be used for dynamic CR monitoring, the small size of neonatal vessels hinders an accurate measurement of the vessel diameter, which is necessary to calculate blood flow within a specific artery.[30] The small vessel size also causes frequent loss of signal, limiting the application of neonatal TCD to static CBF assessments.[31–33]

NIRS exploits the relative transparency of near-infrared light (700–950 nm) in biological tissue and the oxygen-dependent absorption of haemoglobin at different wavelengths to measure $rStO_2$, derived from the changes in concentration of O_2Hb and HHb within the vascular beds (Fig. 3). Fluctuations in cerebral $rStO_2$ can reflect changes in CBF if other determinants of cerebral metabolism and oxygen delivery (i.e., arterial oxygen saturation, haemoglobin concentration, arterial–venous volume ratio, fractional inspired oxygen, tissue oxygen diffusivity) remain relatively constant.[34] NIRS monitoring can be performed non-invasively and continuously for relatively prolonged periods; hence, cerebral $rStO_2$ has been used as a surrogate for dynamic CBF monitoring, mainly for slow CBF changes. The changes in total cerebral haemoglobin concentration (ΔtHb) or tissue haemoglobin index (THI), as a sum of ΔO_2Hb and ΔHHb or directly measured using the isosbestic 805 nm wavelength, have been described as surrogate measurements of cerebral blood volume.[12,35–37]

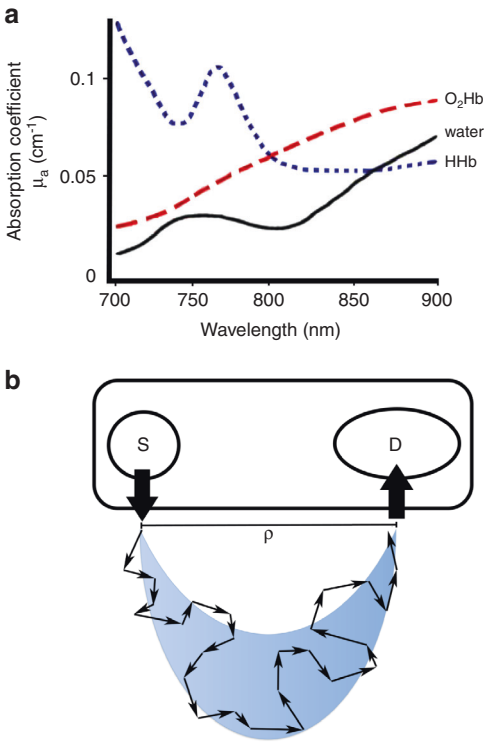

Fig. 3 Near-infrared spectroscopy: absorption spectra and photon trajectory. a Absorption spectra for oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb), and water. **b** Example of photon trajectory through biological tissue. S source, D detector, ρ source-detector distance. The shaded part highlights the area crossed by the photon. Adapted with permission from Martini et al.[172].

The interaction between CBF and CPP is mediated by cerebrovascular resistance as follows, using an analogy of Ohm's law:

$$\mathrm{CBF} = \frac{\mathrm{CPP}}{\text{Cerebrovascular resistance}}$$

Cerebrovascular resistance is determined by the vascular tone of the arterial smooth muscle cells. During brain development, the muscularis layer of the extra-striatal arterioles is initially limited to the pial vessels and superficial penetrators; consequently, in preterm infants, cerebral vasoreactivity occurs predominantly in the superficial and peripheral parenchyma of the brain.[38]

CPP is dependent on ABP and intracranial pressure. As intracranial pressure is assumed stable in neonates because of the open cranial sutures, the slow waves of ABP can presumably be used as a surrogate for low-frequency CPP changes. With high-frequency CPP changes and oscillations (>0.20 Hz), the autoregulatory processes become less able to stabilise CBF in the face of changing CPP.[39] Therefore, these fast CPP oscillations are passed along unimpeded into CBF oscillations. In contrast, slower frequency oscillations (<0.20 Hz, but most effectively <0.05 Hz) can be counteracted by the cerebral arterioles and are dampened.[40,41] Hence, continuous measurements of slow rhythmic oscillations in ABP and CBF have been used to assess the integrity of pressure-flow autoregulation[36,42–46] and, in different neonatal cohorts, have also identified individual optimal ABP (ABPopt) ranges within which autoregulatory mechanisms are most effective, defined by the lowest values of the related CR coefficient indicating functional reactivity.[47–52] Continuous ABP monitoring requires an indwelling arterial catheter[53] and may not always be feasible. To date, evidence on the use of non-invasive continuous monitoring for blood pressure (e.g., beat-to-beat

finger arterial devices) to assess neonatal pressure-flow autoregulation is limited,[54,55] and the reliability of non-invasive blood pressure monitoring against invasive methods needs further improvements.[56,57] Using blood pressure data measured non-invasively by arm cuffs at 15 min after birth, functional pressure-flow autoregulation was demonstrated in term neonates during the immediate postnatal transition, but not in preterm infants at this early phase.[58]

Being a direct determinant of cardiac output, heart rate (HR) can be considered a surrogate of systemic blood flow. Since continuous HR monitoring is non-invasive and universally available, HR can represent an alternative input signal to assess CR in response to systemic blood flow changes. A moving correlation coefficient between cerebral $rStO_2$ and HR (TOHRx) has been proposed for CR monitoring in preterm infants, with rising values indicating loss of CR.[47,48,59–61] Low or negative TOHRx values have been used to define ABPopt ranges during the first 24 h after birth.[48] The recent neonatal application of non-invasive bedside devices for continuous cardiac output monitoring may facilitate the investigation of CR to systemic blood flow; current data, however, are limited. Two reports have found no association between cardiac output and cerebral $rStO_2$ in term infants immediately after delivery[62] or at different sleep positions.[63]

$PaCO_2$ can also be used as an input to evaluate CBF-CO_2 reactivity.[8,64] End-tidal ($etCO_2$) or transcutaneous CO_2 (tCO_2) monitoring allow continuous, non-invasive estimation of $PaCO_2$. The relationship between tCO_2 and THI in neonates has been evaluated by Dietz et al.,[65] who documented a trend towards increased CO_2 reactivity in healthy term neonates between days 1 and 4, whereas Aly et al.[66] found that lower gestational age (GA), mechanical ventilation and increased $PaCO_2$ were associated with stronger CO_2 reactivity in the first week of life in preterm infants, with possible implications on the risk of brain injury. $EtCO_2$ fluctuations have also been associated with concomitant changes in cerebral $rStO_2$ and electroencephalographic brain activity.[67] Other studies using punctual $PaCO_2$ from blood gas analysis yielded variable results: in preterm infants, Kaiser et al. observed a progressive loss of pressure-flow autoregulation for $PaCO_2$ ≥45 mmHg during the first week of life,[8] whereas Hoffman et al. failed to demonstrate an overall association between $PaCO_2$ and pressure-flow autoregulation during the transitional period.[68] During the immediate postnatal period (i.e., 15 min after birth), Wolfsberger et al. observed that the vasodilative effect of $PaCO_2$ on cerebral $rStO_2$ was less pronounced in preterm compared to term neonates.[69]

Electroencephalographic techniques have been used to investigate CBF responses to neurophysiological changes. In preterm neonates, Roche-Labarbe et al. described that spontaneous bursts of electroencephalographic activity were coupled to a haemodynamic response characterised by an O_2Hb decrease, followed by an increase and then a return to baseline.[70] Tataranno et al. documented a decreased cerebral $rStO_2$ and increased tissue oxygen extraction in extremely preterm infants with increasing intensity of spontaneous brain activity.[71] Seizures are paroxysmic bursts of abnormal electrical brain activity. Available neonatal data during different types of seizures consistently report a reduction of cerebral $rStO_2$,[72–74] followed by a variable $rStO_2$ increase.[73,74] The observed $rStO_2$ reduction was associated with an O_2Hb decrease and an HHb increase mimicking a 'negative functional response' pattern,[73] consistent with the elevated oxygen consumption associated with seizures which exceeds cerebral oxygen delivery.

Notably, CR assessment is only reliable if considerable variability in the input signal is present; if there is no variation, dependency cannot be determined. Some researchers have proposed adding more weight to epochs with high variability to correct for this factor.[75–77] Furthermore, when compared to outer input signals such as those derived by electroencephalographic or electrocardiographic techniques, some NIRS instruments may have a lower sampling rate; this may affect the calculation accuracy of some CR metrics such as those for neurovascular coupling, especially for long-term monitoring periods.[19,25,78]

PROPOSED MATHEMATICAL METHODOLOGIES FOR CR ASSESSMENT

Recent overviews, which also provide specific methodological details of the studies included, have confirmed the feasibility of examining CR in the neonatal population.[79,80] To date, however, there is no clinical gold standard methodology for CR assessment; this is reflected in the numerous mathematical methods used for these purposes. These methodologies have mostly been applied to the investigation of pressure-flow autoregulation. Signal processing techniques for assessing neurovascular coupling have recently been reviewed by Hendrikx et al.[19] and will not be addressed in this review.

Invasively measured ABP and cerebral $rStO_2$ as surrogates for CPP and CBF, respectively, are included in different mathematical models to address pressure-flow autoregulation. The lack of standardisation on different levels in the quantification of pressure-flow autoregulation (Table 1) hinders the reproducibility of studies that have related the analyses with clinical outcomes.

To study cerebral autoregulation, a synchronised capture of the physiological signals from multiple monitoring systems into a single aggregated file is required. Several available data capture platforms compatible with current NIRS monitors have been recently summarised by Vesoulis et al.[81] A major step in pre-processing of the acquired data is the removal of artefacts; although this essential component is often performed manually, ideally a reliable automated approach would speed up this stage, avoid any biases, and enable real-time analysis. As two key assumptions for the use of $rStO_2$ as a surrogate for CBF are stable SpO_2 and cerebral metabolic rate ($CMRO_2$), correction for SpO_2 and $CMRO_2$ would ideally also be necessary. The total cerebral haemoglobin concentration has been proposed by Grubb et al. as a surrogate for CBF independent of the $CMRO_2$.[82]

Pressure-flow autoregulation analysis, making use of the spontaneous oscillations in cerebral oxygenation and ABP, has been explored both in the time domain and frequency domain by correlation and coherence analysis, respectively. These approaches assume that the physiological parameters are considered stationary signals.

Time-domain methods

The time-based method of Pearson correlation (*r*) is the most straightforward approach. The correlation coefficient between $rStO_2$ and ABP is used as a cut-off value to assess the presence or absence of pressure-flow autoregulation (the closer to 0, the higher the autoregulatory capacity); significant positive correlation is then considered to represent pressure-passive cerebral circulation in that epoch.[83–88] A question remains whether the cerebrovascular transit time (i.e., the time needed for cerebral $rStO_2$ to fully respond to a CBF change) is considered. In this regard, the moving correlation coefficient between cerebral $rStO_2$ and ABP, which has been validated in hypotensive piglets and has been shown to correlate with TCD measurements of pressure-flow autoregulation in adult patients,[44] has been largely used in neonatal clinical observational studies.[85,89–92] The percentage of epochs with impaired pressure-flow autoregulation (defined as *r* above a predefined threshold), the strength of correlation, but also the amount of *r* variability during measurement can be assessed.[93] These principles have been applied to other NIRS-based parameters to study pressure-flow autoregulation. For example, the moving correlation between THI and ABP has been used to determine individualised ABPopt.[49,50,52,94,95] Similarly, the Pearson correlation between THI and tCO_2 has been used to investigate CR to CO_2 in the neonatal population.[65,66]

Table 1. Variability on different levels in the quantification of cerebrovascular reactivity in infants.

Monitoring parameters							
CPP-related variables		*NIRS-measured CBF-related parameters*			*Other physiological variables*		
ABP (mean, systolic, diastolic)		$rStO_2$			SpO_2		
Heart rate		$HHb/O_2Hb/HbT/THI$			tCO_2		
					Temperature		
Data capture methods							
Synchronised capture of physiological parameters with time stamp							
Separate device downloading							
Patient-based central-hub strategy with laptop							
Pre-processing of data							
Data preparation		*Artefact reduction methods*[124,156–159]			*SpO_2 correction method*		
Downsampling		Automated or manual			No SpO_2 correction		
Filtering		Missing values			<5% SpO_2 correction		
		Out-of-range values			Partial coherence		
		Motion artefacts			Partial directed coherence		
					Oblique subspace projections		
					Fractional tissue oxygen extraction (FTOE)		
Data characteristics							
Duration of measurement							
Sample frequency							
Choice of epoch length							
Choice of percentage overlap							
Choice of mathematical model							
Time domain		*Frequency domain*		*Time-frequency domain*		*Non-stationary methods*	
Method	*Proposed threshold for impaired CR*	*Method*	*Proposed threshold for impaired CR*	*Method*	*Proposed threshold for impaired CR*	*Method*	*Proposed threshold for impaired CR*
Linear regression	Slope, breakpoint[134]	Coherence (COH)	0–0.7 (or with Monte-Carlo simulations)[45,46,75–77,110,112,129,157,160–163]	Bivariate auto-regressive coherence (BiAR-COH)	0.58[98]	Continuous wavelet transform or cross-correlation	>0.5[164]
Correlation coefficient (*r*)	>0.4–0.5[83–88,139]	COH + transfer function (TF) gain	No	Partial directed coherence method (PDC)	0.554[69]	Bivariate phase rectified signal averaging (BPRSA)[165]	No
Moving correlation coefficient COx or TOx	>0–0.5[85,89–92,96]	TF phase	No				
Moving correlation coefficient HVx	No	Logarithmic TF gain	No				
Moving correlation coefficient TOHRx	No						

ABP arterial blood pressure, *CBF* cerebral blood flow, *CPP* cerebral perfusion pressure, *CR* cerebrovascular reactivity, *HHb* deoxygenated haemoglobin, *HbT* total haemoglobin, *NIRS* near-infrared spectroscopy, *O_2Hb* oxygenated haemoglobin, *THI* total haemoglobin index, *SpO_2* peripheral arterial oxygen saturation, *tCO_2* transcutaneous CO_2.

Frequency-domain methods

Coherence analysis has been applied to explore the relationship between NIRS measurements and ABP changes in the frequency domain.[96] Notably, according to the Nyquist theorem, the sampling frequency of the collected data needs to be at least twice the highest frequency of interest in the signal. Similar to time-domain methods, a predefined threshold is used to define impaired pressure-flow autoregulation (the closer to 0, the higher the autoregulatory capacity). To correct for different epoch lengths and sample frequencies, Monte-Carlo simulations are performed to identify significant coherence in the given data segments;[75,97] adaptations to the basic model of coherence are also made.[76,98] Coherence describes the impairment of pressure-flow autoregulation quantitatively. The degree of dependence between two variables (e.g., ABP and $rStO_2$) is measured (no units), and by performing transfer function analysis, the gain and phase are calculated. The gain estimates the degree of this impairment by describing the magnitude of change in the output signal (e.g., $rStO_2$) in relation to a unity change in the input signal (e.g., ABP) at a given frequency. However, causality, i.e., what signal induces changes in the other signal, cannot be established by these methods. Wong et al.[45] first used coherence and gain to assess $rStO_2$-derived pressure-flow autoregulation in sick infants. This method was later validated by Hahn et al. in piglets.[99] Transfer function with logarithmic transformation of the gain coefficient to provide the amplitude of the dampening response is described by Vesoulis et al.[100] The phase describes the time delay between coherent oscillations of the two signals and can be seen as an additional factor in pressure-flow autoregulation analyses. Pressure-flow autoregulation can be studied in different frequency bands, ranging from ultra-low to high-frequency bands. Low-frequency bands correspond to slow oscillations in ABP and $rStO_2$. Slow and prolonged periods of hypotension or hypertension of higher magnitudes are considered to be more injurious than fast and transient ABP changes of small magnitudes ('high-pass filter' principle of pressure-flow autoregulation).[101]

Time-frequency methods

Since biological signals tend to be non-linear and non-stationary, alternative methods based on linear equations, such as wavelet cross-correlation, have also been described.[102] This approach incorporates a time element to frequency analysis. It makes no assumption about the stationarity of input signals, providing a framework for the analysis of non-stationary effects in cerebral haemodynamics. Another time-frequency method, defined as bivariate auto-regressive coherence (BiAR-COH), has been proposed by Riera et al.[98] The main difference between the BiAR-COH and standard coherence methods is that the former demands both temporal and frequency dependence, whereas coherence only evaluates frequency dependence. This key feature discriminates changes in the two signals that are closely related in time from those that are not time-related and, therefore, have no mutual dependence. The same authors introduced the partial directed coherence (PDC) method to address the condition of directionality,[76] so that the system is forced to consider only those events in which changes in CPP induce changes in CBF. Therefore, this approach not only analyses pressure-flow autoregulation, but also infers causality.[76]

IMPAIRED CEREBROVASCULAR REACTIVITY AND NEONATAL OUTCOMES

Impaired CR is a marker of disease severity and adverse outcome, both in term[85,103–110] and preterm infants.[60,76,83,84,91,98,111–113] The patient populations most often studied are neonates with hypoxic-ischaemic encephalopathy (HIE) and preterm infants during the postnatal transition, which will be discussed hereafter; specific study details on these populations are available in other reviews.[80,114,115] Insights on other neonatal conditions are also available in recent targeted reviews.[2,116]

There is longstanding evidence of the association between perinatal hypoxia-ischaemia and altered CR, resulting in hypoxia-ischaemia-reperfusion injury.[117–119] Cerebral hypoxia-ischaemia induces compensatory overproduction of NO,[120] leading to persistent cerebral vasodilation that may disrupt the vessels' autoregulatory capacities (the so-called vasoparalysis).[115] Upon reperfusion, the disrupted CR results in a significant increase in CBF with no change in $CMRO_2$.[121] In animal models of hypoxia-ischaemia, this cerebral hyperaemia has been associated with histopathological evidence of brain damage.[106,115] Consistent evidence of post-asphyxial cerebral hyperaemia has been obtained from human neonates with HIE using NIRS.[103,115,122,123] This CBF increase positively correlates with the severity of the ischaemic hit, and is accompanied by an impaired CR to acute ABP and CO_2 changes.[119] The burden of cerebral hyperaemia and of CR impairment was greater in infants who later developed brain injury on MRI or showed poorer neurodevelopmental outcomes.[85,103–108,110,124] Using wavelet coherence between NIRS and electroencephalographic signals, Das et al.[109] recently showed that HIE infants with MRI brain abnormalities had poorer neurovascular coupling during the first 24 h compared to those with normal neuroimaging. Notably, the cerebral $rStO_2$- electroencephalographic coherence during this early period was superior to the Sarnat score in predicting abnormal brain MRI.

Given the altered CR following perinatal asphyxia, defining ABPopt ranges of pressure-flow autoregulation is particularly important. Prolonged ABP deviations below ABPopt during the hypothermic treatment have been associated with increased MRI abnormalities in both the deep grey matter[51,52] and white matter.[50] Infants with more prolonged deviations below ABPopt also had greater motor and cognitive impairments at 21–32 months.[49] Based on this evidence, monitoring pressure-flow autoregulation to establish and target ABPopt ranges with a tailored haemodynamic management (e.g., adjusting pharmacological cardiovascular support) is potentially an adjunctive neuroprotective strategy in neonatal HIE.

In the preterm population, the cardiovascular changes occurring during the first 72 h after birth, which define the so-called transitional period, are often associated with a significant haemodynamic instability together with CBF fluctuations that may cause disruption of the germinal matrix endothelium, increased intravascular pressure and[125] result in intraventricular haemorrhage (IVH).[126] Accordingly, specific NIRS patterns of cerebral haemodynamics have been reported in infants developing this complication, characterised by reduced cerebral $rStO_2$ during the first 24 h[60,91,127,128] followed by a transient increase,[60,127] which suggest the hypoperfusion-hyperaemia alternance.

Numerous NIRS studies have shown impaired CR in preterm infants developing IVH.[60,61,76,83,84,91,98,111,112,129] Severe IVH development has been associated with a significantly higher time burden of a pressure-passive circulation on day 2, which was also the median age at IVH detection.[84] An independent association between high-magnitude cerebral pressure-flow passivity in the low-frequency range and IVH development has also been found.[112] With regard to ABPopt, infants with greater deviations below or above ABPopt ranges had higher IVH rates compared to those whose ABP laid close to optimal ranges during the transition.[47,48] Significantly higher TOHRx values were also reported in infants who developed IVH compared to those who did not.[60,61] In contrast, one study observed lower amplitudes of cross-correlation, semblance and gain between cerebral $rStO_2$ and HR, measured by wavelet analysis, in a small number of preterm infants developing IVH/pulmonary haemorrhage compared to those who did not, possibly reflecting the extreme haemodynamic instability associated with haemorrhages.[130]

The link between CR indices and systemic blood flow, as well as their relationship to IVH has also been reported. Low superior vena

Table 2. Proposal for a series of feasibility trials aimed at addressing the currently open questions on neonatal cerebrovascular reactivity (CR).

1. Which surrogate marker for CPP is most valid and feasible to use in neonates?
• Animal research into the most promising surrogate marker for CPP (e.g., mean, systolic, diastolic ABP and heart rate) may need to be performed to support the experts' consensus. • To assess and compare the relations between NIRS measurements and the different surrogates of CPP, including mean, systolic, diastolic ABP and heart rate, and possibly using transcranial Doppler sonography in a subset of infants to simultaneously assess CBF velocity as an alternative measure of CPP for comparison. • The ultimate choice for the optimal surrogate marker may differ between preterm and term infants and in relation to different clinical conditions with different haemodynamic impacts (i.e., sepsis, hypoxic-ischaemic encephalopathy, congenital heart disease).
2. Which mathematical approach relating cerebral $rStO_2$ to the CPP surrogate marker is most sensitive and most robust to detect impaired CR and predict neurological outcome?
• To study reproducibility, predictive capability and inter-method comparisons between two or more different methods in both term and preterm infants' databases using both short-term (e.g., ischaemic or haemorrhagic) cerebral injury and long-term neurodevelopment associated with impaired CR as an outcome.
3. How should clinical care be guided by the assessment of CR?
• To develop a clinical intervention guideline based on current literature, similar to the SafeBoosC trial. This may entail keeping ABP (or another measure for CPP) between certain individual levels as determined by the bedside CR assessment, while at the same time ensuring $PaCO_2$ and other influencing parameters within the normal range. • A randomised trial entailing an intervention group with bedside real-time CR assessment using dedicated software tools (e.g., ICM+®), combined with a clinical intervention guideline vs. a control group with blinded CR assessment; evaluating short-term cerebral injury and later neurodevelopment will assess the efficacy of CR monitoring in improving neurological outcomes of at-risk neonates. • The use of artificial intelligence on large datasets may contribute to define in hindsight the most valid approach for outcome prediction.
4. How can we improve the accuracy of the CBF surrogate marker in CR studies?
• More sophisticated time-and-frequency domain systems, measuring not only $rStO_2$ but also absolute concentrations of O_2Hb and HHb, have been validated in piglet models[166] and have been explored in neonatal research settings.[122,167–171] • To improve precision, reproducibility and signal-to-noise ratio of NIRS measurements. • To improve probe design and user-friendliness especially for extremely preterm and/or critically ill infants.

ABP arterial blood pressure, *CBF* cerebral blood flow, *CPP* cerebral perfusion pressure, *CR* cerebrovascular reactivity, *HHb* deoxygenated haemoglobin, *NIRS* near-infrared spectroscopy, *O_2Hb* oxygenated haemoglobin.

cava (SVC) flow has been pathophysiologically linked to intracranial bleeding in preterm neonates.[125,131] Low SVC flow infants also had higher BiAR-COH and PDC, indicating impaired pressure-flow autoregulation, and were more prone to developing severe IVH.[76,98] A negative correlation between COx and left ventricular output at 24 h of life in a cohort of neonates that developed IVH has also been reported.[91] These findings align with the report of lower left ventricular output and cerebral $rStO_2$ within the first day of life in infants who later developed IVH,[127] and may reflect CR impairment associated with fluctuations of systemic blood flow before or around the time of bleeding. The association between other factors influencing CR, such as $PaCO_2$ and IVH,[132] warrants further targeted investigations.

DOPAMINE AND IMPAIRED PRESSURE-FLOW AUTOREGULATION: CAUSALITY OR ASSOCIATION?

Circulatory failure and the need for cardiovascular support using inotropic/vasopressor medications have been associated with impaired cerebral pressure-flow autoregulation. Due to its alpha-, beta-adrenergic and dopaminergic activity, dopamine has long been used as a vasopressor-inotrope to support circulation and maintain adequate perfusion of critical organs, such as the brain.[133] Dopamine's impact on cerebral pressure-flow autoregulation, secondary to its effects on vascular tone or inotropism, remains inconclusive. Several NIRS studies reported that, in hypotensive preterm infants treated with dopamine, both CBF and ABP increase together,[134–137] indicating that cerebral pressure-passive circulation or a small positive slope of the autoregulatory plateau[92,134] may persist over a range of ABP. Moreover, time periods with impaired pressure-flow autoregulation in hypotensive infants were reported to increase with dopamine treatment in a dose-dependent fashion.[138–140] However, the methodology and design of these studies could not address whether dopamine directly impaired the autoregulatory capacity or was merely an indicator of illness. In contrast, when dopamine effects were investigated in newborn piglets with induced hypotension, an improvement of cerebral pressure-flow autoregulation at low ABP, proportional to dopamine dose, was observed.[141] Recent data from the HIP trial, where hypotensive preterm neonates were randomly assigned to either dopamine or placebo infusion,[142] reported a significantly impaired pressure-flow autoregulatory capacity in hypotensive compared to normotensive infants, but not in relation to dopamine treatment.[111] This, however, was not an adequately powered study; therefore, no firm conclusions can be drawn. Although currently available evidence suggests that autoregulatory capacity may be impaired by hypotension and its underlying causes rather than by dopamine treatment, larger targeted studies are needed to validate these findings and to define the complex relationship existing between these factors. In addition, data on the impact of other inotropic and vasoactive medications on pressure-flow autoregulation in preterm infants remain very limited and scarce.

DISCUSSION

Current evidence on neonatal CR is based on many observational studies which, over the years, have pointed towards physiological associations between altered CR and an increased risk of brain injury. To move forward towards a preventive and therapeutic approach in neonatal CR research, multiple aspects need to be considered.

First, most of the available neonatal literature is derived from single-centred studies, based on small and heterogeneous cohorts which are under-powered and potentially involve biases and confounders (e.g., different types of brain injury, lack of $PaCO_2$ data, use of different monitoring windows etc.), hindering comparison between studies to quantify the independent impact of CR impairment.

Second, an agreement on the multiple methods proposed for CR estimation is needed. The heterogeneity in the monitoring

devices, recording methods, pre-processing steps and mathematical models applied for CR assessment hampers the identification of possible gold standard methodology that shows the best sensitivity and specificity for outcome prediction. The comprehensive integration of different multimodality monitoring signals, as well as the adoption of the Findable, Accessible, Interoperable, and Reusable approach[143] for an open database with high-resolution data on cerebral $rStO_2$, ABP, HR and standardised outcomes would facilitate the comparison and evaluation of their performances in predicting outcome.

Third, if an acceptable and reliable methodology for CR assessment is agreed upon, continuous real-time monitoring of CR may allow a personalised approach to neonatal intensive care, aimed at optimising CR and reducing neonatal brain injury. Continuous CR assessment combining $rStO_2$, ABP and tCO_2 monitoring should ideally be measured in at-risk neonates. However, such a comprehensive and multi-modal monitoring may be technically challenging (e.g., skin frailty, signal noise, availability of intra-arterial catheter), especially in extremely preterm neonates. In this regard, the validation of CR measurements using less invasive parameters (e.g., HR) as input signals for outcome prediction would facilitate CR monitoring and application in neonatal settings. Further improvements in the design of NIRS probes to suit the fragile skin of extremely preterm infants may also support long-term CR monitoring.

Some of the above aspects have been tackled by adult neurointensive care research groups, especially following traumatic brain injury (TBI), sepsis and stroke.[144–146] In this setting, a Delphi consensus stating that CR status is uniquely dependent on an individual patient at any specific time, excluding the use of universal and absolute thresholds for CPP, was formalised, and a research agenda was proposed to establish and validate CR assessment methods against outcome, together with prospective safety, feasibility and efficacy studies to investigate the application of CR-guided clinical management.[147] Of note, a study in adults with TBI, investigating the feasibility of automated assessment of optimal CPP based on individualised CR monitoring, is currently recruiting.[148–150]

A consensus approach similar to the abovementioned one may help to establish a future research agenda including collaborative clinical NIRS-based trials, targeted to address the current questions on neonatal CR listed in Table 2. These feasibility trials may represent the first step towards a randomised controlled trial based on continuous real-time CR monitoring, using dedicated software and aimed to assess whether a proposed treatment strategy (i.e., actively maintaining ABP within an optimal CR range) may improve neurological and neurodevelopmental outcomes. The goals are to identify infants with CR impairment predictive of brain injury, followed by interventional trials to prevent or correct the CR impairment for neonatal neuroprotection. Indeed, the SafeBoosC trials have pioneered the multi-centred approach in assessing the benefit of clinical interventions to optimise cerebral $rStO_2$ in preterm neonates.[151–155] In this regard, the formation of an international, multicentre working group to coordinate clinical trials and collated data management would support achieving these research targets.

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ADDITIONAL INFORMATION

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