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REVIEW

Measuring cerebrovascular autoregulation in preterm infants using near-infrared spectroscopy: an overview of the literature

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ABSTRACT

Introduction: The preterm born infant's ability to regulate its cerebral blood flow (CBF) is crucial in preventing secondary ischemic and hemorrhagic damage in the developing brain. The relationship between arterial blood pressure (ABP) and CBF estimates, such as regional cerebral oxygenation as measured by near-infrared spectroscopy (NIRS), is an attractive option for continuous non-invasive assessment of cerebrovascular autoregulation.

Areas covered: The authors performed a literature search to provide an overview of the current literature on various current clinical practices and methods to measure cerebrovascular autoregulation in the preterm infant by NIRS. The authors focused on various aspects: Characteristics of patient cohorts, surrogate measures for cerebral perfusion pressure, NIRS devices and their accompanying parameters, definitions for impaired cerebrovascular autoregulation, methods of measurements and clinical implications.

Expert commentary: Autoregulation research in preterm infants has reported many methods for measuring autoregulation using different mathematical models, signal processing and data requirements. At present, it remains unclear which NIRS signals and algorithms should be used that result in the most accurate and clinically relevant assessment of cerebrovascular autoregulation. Future studies should focus on optimizing strategies for cerebrovascular autoregulation assessment in preterm infants in order to develop autoregulation-based cerebral perfusion treatment strategies.

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1. Introduction

More than 10% of all infants worldwide are born preterm, before 37 completed weeks of gestation [1]. These infants are at risk for neurodevelopmental sequelae later in life because of cerebral damage. The pathophysiological mechanism is likely multifactorial and may start before birth and continue for months after birth. During the first days after preterm birth, there are strong indications that cerebral ischemia, due to hypoxia or fluctuations in cerebral blood flow (CBF), might play a major role in brain injury and the development of motor, cognitive, and behavioral impairment in a significant proportion of these infants in later childhood [2].

The healthy mature brain has its own protective mechanism in which CBF is kept constant while cerebral perfusion pressure (CPP) varies, due to slow adaptations in arteriolar vasoconstriction and dilatation. This is known as cerebrovascular autoregulation. The preterm brain is particularly vulnerable to low CBF state leading to silent ischemic events and the radiological diagnosis of periventricular leukomalacia (PVL) [3]. On the other hand, increased CBF may result in hyperperfusion and subsequent germinal matrix or intraventricular hemorrhage (GMH/IVH) [4]. One of the suggested factors for the perfusion-related brain injury of the preterm infant is attributed to a lack of robust cerebrovascular autoregulation, vividly described by Haruda [5] in 2001:

> *The structure of normal adult arteries resembles automobile tires, tough and elastic. In contrast, the vessels of the germinal matrix of prematures resembles an inner tube, with no surrounding rubber tread or steel cord, (. . .) disasters waiting to happen. (. . .) This is why exquisite blood pressure control in the neonatal intensive care is crucial, and without autoregulation, is like walking a tightrope in a hurricane.*

This quote was a response to the article by Tsuji et al. to underline the importance of realizing and recognizing the absence of cerebrovascular autoregulation in preterm infants [6]. Haruda hypothesized that the histological nature of the arteries in the germinal matrix – lacking smooth muscle cells – is the main cause for this absent or immature autoregulation.

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In reply, the authors stated that,

> *this lack of muscularis includes virtually all arterial vessels penetrating the cerebral parenchyma in the third trimester of human gestation. This is not likely the whole story, (…) there is good evidence that in some premature infants there is a degree of intact cerebrovascular autoregulation.(…) The use of continuous near-infrared spectroscopic measurements of the cerebral circulation at least gives us a start by identifying those infants with the abnormality and therefore with the highest risk for ischemic and hemorrhagic injury.* [5]

The above quote clearly describes the issues of absent or immature capacity of the premature cerebral arterioles to adapt to systemic challenges like significant arterial blood pressure (ABP) fluctuations. They have led to several observational studies investigating different concepts and clinical factors associated with impaired cerebrovascular autoregulation in preterm infants. We will present the current knowledge on cerebrovascular autoregulation in preterm infants below to provide substantial background information before getting to our review focus, reporting the results of our main literature search on cerebrovascular autoregulation assessment using near-infrared spectroscopy (NIRS) in preterm-born infants, in text and in Table 1.

2. Cerebrovascular autoregulation

2.1. Concepts of static and dynamic autoregulation

Cerebrovascular resistance is regulated through changing the vascular tone of the cerebral arterioles, yielding vasodilation in case of low CPP and vasoconstriction in case of high CPP [4]. The regulation of vascular resistance is believed to have individual upper and lower thresholds [7]. The exact thresholds for the upper and lower limit of cerebrovascular autoregulation have not been identified, partly due to the fact that most clinical studies rely on spontaneous ABP fluctuations which may or may not be within the CPP range in which autoregulation is functional. Also, these thresholds might differ between and within infants and possibly depend on multiple factors, such as gestational and postnatal age. In neonates, intracranial pressure (ICP) cannot be measured directly like in adults. Because of the open fontanel, it is assumed that ICP is low, close to atmospheric pressure. Therefore, ABP is often used as the surrogate for CPP. The theoretical background is explained in Figure 1. It shows the relationship between CBF and ABP in preterm infants for impaired and intact autoregulation. This concept is largely adapted from insights from adult studies [8]; CBF is suggested to be stable (plateau) over a wide ABP range, reflecting 'intact' static cerebrovascular autoregulation (lower panel in Figure 1). Noteworthy, in adult studies, it has been suggested that this plateau might not be completely horizontal [9,10]. Absent autoregulation is often represented by a strong linear relationship between CBF and ABP (upper panel in Figure 1).

Beyond the thresholds, a status of 'pressure passivity' occurs with CBF following changes in CPP directly. Theoretically, this could lead to either relative cerebral hypoperfusion (ischemia) or hyperperfusion (edema or hemorrhage).

Cerebrovascular autoregulation can be described in two dimensions which the literature terms 'static' and 'dynamic' pressure autoregulation. Static autoregulation refers to adaptations of the cerebrovascular resistance in a steady-state and controlled situation, which means an evaluation of CBF at several steady ABP levels. Experience was initially gained by data from animal models like preterm lambs [11,12]. Early techniques that were used to study static autoregulation in preterm infants are the xenon clearance (^{133}Xe) technique or the oxyhemoglobin (HbO_2) method by NIRS [13–15].

The dynamic autoregulation concept refers to the evaluation of the faster cerebrovascular responses after spontaneous and relatively brief changes in ABP [16]. Traditionally, transcranial Doppler (TCD) ultrasound is used to measure cerebral blood flow velocity (CBFV) continuously at the bedside to determine dynamic autoregulation [17,18]. Limitations of this noninvasive technique are the assumption of a constant intracerebral vessel caliber, not taking into account the angle of vessel insonation and difficulties with obtaining long and stable recordings.

Another noninvasive way for continuous CBF assessment is measuring the regional cerebral oxygen saturation by NIRS. The NIRS technology is especially suitable for preterm infants with thin skulls. Using NIRS for the assessment of cerebrovascular autoregulation will be addressed in depth in this review.

Notably, changes in the cerebral vessel tone and resistance are influenced by many more factors than ABP alone. Many physiological and biochemical mechanisms may interact and affect this complex mechanism. Accordingly, autoregulation results should be reviewed with changes in pH, $PaCO_2$, PaO_2, metabolism, blood glucose, sympathetic activation, and effects of neurovascular coupling [4,15,19,20] taken into account. We refer to other reviews for more in-depth information on these important confounders affecting cerebral vasoreactivity [4,7,21–23].

3. Cerebrovascular autoregulation in preterm infants

First reports on impaired cerebrovascular autoregulation in preterm infants dated from 1979 to 1980. Lou et al. reported on 19 infants with respiratory distress syndrome (RDS) in combination with perinatal asphyxia showing a linear relationship between CBF (measured by the ^{133}Xe technique) and systolic ABP within the first hours after birth [24]. Milligan et al. reported on five preterm infants with increasing CBF values (measured by jugular venous occlusion plethysmography) after receiving either whole blood or blood product transfusions resulting in increased mean arterial blood pressure (MABP) levels of 5–14 mmHg on days 1 till 4 after birth. All infants developed subsequent intracranial hemorrhages [25].

3.1. Autoregulatory capacity

There is an ongoing debate on whether cerebrovascular autoregulation is present in preterm infants at birth or whether it slowly develops postnatally. Conclusions are limited by the fact that cerebrovascular autoregulation can also be impaired due to illness or therapeutic interventions. Two studies found intact cerebrovascular autoregulation in all of the preterm infants studied, either undergoing high-frequency oscillatory

ventilation [26] or treated for hypotension [27]. This was based on the absent relationship between CBF or cerebral fractional oxygen extraction (measured by NIRS) and ABP. In contrast, Boylan et al. studied dynamic autoregulation by measuring CBFV and ABP and found it to be totally absent in both 'high-risk' (defined as having cerebral pathology, e.g. seizures or IVH) and control preterm infants [28]. Soul et al. found impaired cerebrovascular autoregulation in about 20% of the recording time using NIRS in 87 out of 90 very preterm infants during the first 5 days after birth [29]. Other studies also reported on fluctuating autoregulation impairment during the first days after birth [6,30–33].

3.2. Clinical factors

Clinical factors related to impaired cerebrovascular autoregulation are lower gestational age (GA) [29,34,35], lower birth weight (BW), lower glucose levels [29,34,36], higher clinical risk index for babies (CRIB) score [34], increased infant mortality [34,37], and higher $PaCO_2$ levels [15,38,39]. Perinatal risk factors such as pregnancy induced hypertension; antepartum hemorrhage and placental infarction are also associated with impaired cerebrovascular autoregulation [29]. Other pathologies associated with impaired autoregulation include RDS [33] and necrotizing enterocolitis [40]. Infants who underwent surgical ligation of patent ductus arteriosus (PDA) were found to have more impaired autoregulation during the first 6 h after surgery compared to those with PDA treated conservatively with medication [32]. Associations between the development of cerebral pathology and impairment of cerebrovascular autoregulation have been reported. Tsuji et al. and O'Leary et al. reported that dynamic autoregulation impairment was associated with an increased risk of developing GMH/IVH or PVL [6,41]. Alderliesten et al. found a statistically significant correlation between regional cerebral oxygen saturation (rSO_2) and ABP, suggestive of impaired autoregulation, before the development of mild-to-moderate IVH. The high correlations maintained after the development of severe IVH [42]. It is unknown whether these findings are the direct result of the pathologies or related to perioperative conditions and medications (e.g. vasopressors and anesthetics). Finally, being born after intrauterine growth restriction seems to affect cerebral circulation, possibly through additional autoregulatory mechanisms, that results in redistribution of blood in favor of the brain and at the expense of organs such as the kidneys or intestines [43–45].

3.3. Autoregulation thresholds

Even though several studies have studied cerebrovascular autoregulation and hypotension, static upper and lower thresholds of ABP for impaired autoregulation in preterm infants are largely unknown (see also Figure 1). Munro et al. reported that the lower threshold in MABP for cerebrovascular autoregulation, measured by NIRS, might be at 29 mmHg for preterm infants with a GA ranging from 23 to 30 weeks [46]. Other studies were not able to define a clear lower threshold for their cohorts but used a large change in magnitude or percentage of time of impaired cerebrovascular autoregulation to define dangerous MABP levels [29,30]. In contrast, Binder et al. found that a 1-h hypotensive episode (defined as an MABP below the infant's GA) did not affect NIRS rSO_2 significantly in preterm infants with a GA <37 weeks [47].

4. NIRS in preterm infants

4.1. Technique

Since the turn of the millennium, NIRS has been introduced for bedside cerebrovascular autoregulation assessment [6]. This technology is based on the fact that biological tissues are relatively transparent to near-infrared (600–900 nm wavelength) light. By shining a near-infrared light through the thin skin and skull of a preterm-born infant, the amount of oxygenated (HbO_2) and deoxygenated hemoglobin (HHb) can be assessed from the reflected light detected by sensors. From previous studies, it was estimated that the depth of the signal is at least between 15 and 20 mm, enough to reach into the cerebral white matter of these infants [48,49]. Using NIRS, regional HbO_2, HHb, total Hb ($HbT = HbO_2 + HHb$), and difference Hb ($HbD = HbO_2 - HHb$) in the underlying cerebral tissue can be measured. Spatially resolved techniques or the multi-distance approach allows for calculating the ratio of HbO_2 to HbT, expressed by the various manufacturers as the tissue oxygenation index (TOI, %) [50] or the regional oxygen saturation (rSO_2, %), respectively [51]. Assuming a relative constant cerebral metabolism and therefore oxygen consumption as well as a stable venous and capillary blood volume, it is thought that trends in rSO_2 or TOI reflect trends in regional CBF [52].

4.2. Limitations

NIRS can be used bedside, continuously and noninvasively, by placing a sensor on the infant's forehead. Data are shown real time and can be stored off-line for analysis. However, the NIRS technique also has its limitations. It measures only part of the forebrain, where it measures tissue oxygen saturation which represents a weighted average of arterial, capillary, and venous blood. Lacking a gold standard for tissue oxygenation in preterm infants, these tissue-based values have only been validated comparing them to venous saturations, mostly in older children and adults. Though relatively accurate, repeatability of NIRS oximetry, especially after replacement of the sensor, is rather limited with changes up to 8%. This lack in precision hampers clinical decision-making [53]. It is unclear how this affects measurements of cerebrovascular autoregulation using NIRS. One also has to keep in mind that cerebral oxygenation is both GA and postnatal age dependent. In a study in 100 relatively healthy infants, born after a GA between 30 weeks and term age, a GA-dependent cerebral oxygenation in the first 6-h after birth was observed, with higher rSO_2 in the younger group [54]. On the other hand, average $rScO_2$ increased with GA (1% per week) in 999 very preterm infants (<32 weeks), the first 72 h of life [55]. How this relates to measures of cerebrovascular autoregulation remains unclear as well. More details regarding the NIRS technique and its properties and limitations have been described previously in more detail [53].

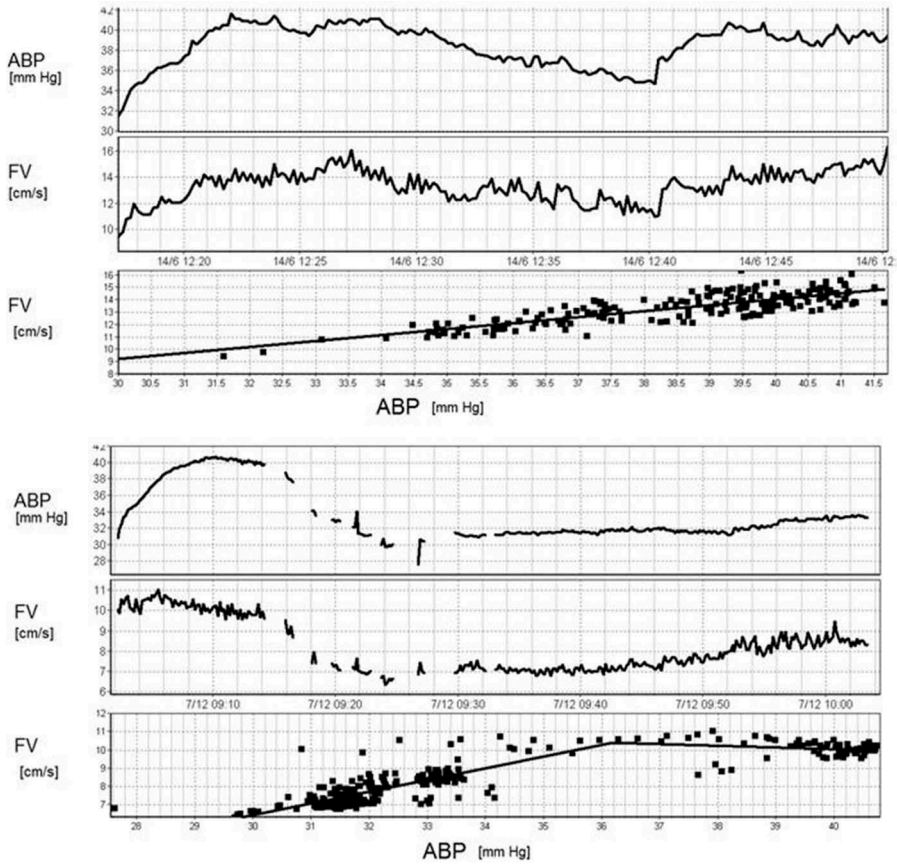

Figure 1. Relationship between TCD blood flow velocity and mean ABP in neonates. Upper panel: completely impaired autoregulation. Lower panel: intact autoregulation is suggested above the (lower) ABP threshold of 36 mmHg. From the material previously presented by Rhee et al J Perinat 2014; 34; 926–931. Abbreviations: ABP; arterial blood pressure, FV; flow velocity.

4.3. Cerebrovascular autoregulation and NIRS

Theoretically, a negative relationship between the input signal (represented by CPP or ABP) and fluctuations in the output signal (NIRS parameters) suggests an active or intact cerebrovascular autoregulation. However, there is a lack in consensus on the exact definition or thresholds for impaired cerebrovascular autoregulation and in which conditions NIRS can be used to represent changes in regional CBF. Furthermore, different types of methods and mathematical approaches, measuring times, frequency bands, and outcome measures are used to describe or validate the autoregulation status.

4.4. Review focus

After this extensive background regarding cerebrovascular autoregulation in preterm infants, we will now focus on the most common methods of cerebrovascular autoregulation assessment using bedside NIRS-derived signals in preterm-born infants.

5. Review methods

To include all relevant original research articles for this review, we performed a PUBMED/EMBASE database search using the search terms '((((premature infant[MeSH]) AND cerebrovascular autoregulation) OR ((premature infant[MeSH]) AND cerebral autoregulation) OR ((premature infant[MeSH]) AND near infrared spectroscopy AND reactivity))). Further inclusion criteria for the retrieved articles were 'written in English' and 'published from 01-01-2000 onwards.' We checked for relevance by assessing the title and the abstract. There were 94 hits of which we selected 22 articles based on following criteria: being a clinical research article, studying/measuring cerebrovascular autoregulation by NIRS, performed in a clinical setting, and studying preterm infants. Furthermore, we added three relevant articles from screening the references of the 22 retrieved articles, based on the same criteria as stated above, and focusing on the (mathematical) methodology. This resulted in 25 articles altogether, of which the details are summarized in Table 1.

6. Results

The results of the literature search are displayed in Table 1. Table columns correspond with the following six paragraphs.

6.1. Characteristics of patient cohorts

6.1.1. Timing

Tsuji et al. were the first to show that NIRS can be used to identify preterm infants with impaired cerebrovascular

Table 1. Overview of the results from the literature search, presented in chronological order.

Author/ year of publication	Characteristics of patient cohorts (number of infants, GA, age at recording, and specific characteristics)	Input parameters (all using spontaneous fluctuations)	Output parameters (NIRS device and accompanying signal, sampling time/rate, and setup)	Definition for (impaired) autoregulation	Methods of measurement: -Duration of measurement -Duration of single epoch -Mathematical approach -Frequency band -% overlap	Clinical implication/main results; data interpretation by the authors
Stammwitz 2016	*N* = 31 26–32 weeks <6 h, 12–16 h, 24–28 h, 68–76 h Stable hemodynamics, most ventilated Clinical setting	MABP HR	Critikon Cerebral Oxygenation Monitor 2001: O_2Hb, HHb, tHb, OI 2 Hz Sensor was placed frontoparietally.	Not explicitly defined	≥12-min epochs without artifacts 0–0.01 Hz, and 0–0.1 Hz frequency. Coherence spectra between tHb or OI and MABP or HR (both appeared interchangeable).	Low coherences during the first 24 h were associated with unfavorable outcome: IVH grade ≥3, abnormal MDI, and mortality.
Kleiser 2016	*N* = 4 26–33 weeks 1–4 weeks Clinical setting	HR, SpO_2	Self-developed multi-distance NIRS (OxyPrem): StO_2 and FTOE Optode was positioned over the left prefrontal cortex	Not explicitly defined	Nonlinear regression based on alternating conditional expectation and maximal information-based nonparametric exploration.	High nonlinear correlation between HR and FTOE in one neonate with reduced health status.
da Costa 2015	*N* = 60 23–32 weeks 5–228 h Clinical setting	MABP HR	NIRO200NX: TOI 10-s averages of HR and TOI Sensor placed on one side of the temporoparietal area of the infant's head.	Lowest TOHRx represents maximal autoregulation within infants.	2 h (with 1-min update) TOHRx: linear correlation coefficient over 5-min epochs with 1 min moving window after removal of artifacts and low-pass filtering and downsampling of the data resulting in one sample every 10 s.	Deviation from MABP at strongest vascular reactivity is related to poor outcome and intraventricular hemorrhage (retrospectively).
Eriksen 2015	*N* = 60[a] 27 ± 1 weeks Day 1 38% ventilated Clinical setting	MABP	NIRO 300: TOI Sampling rate 0.1 Hz Probe secured to the frontotemporal or frontoparietal region of the head with a flexible bandage.	COx ≥0.4 and coherence ≥0.5	Linear correlation (COx) 5-min epochs with 1 min (80% overlap) moving window. Moving coherence: 0.003–0.04 Hz frequency band. 10-min epochs with 50% overlap. TFA coherence and gain. Aim: to describe the relation between time- and frequency-domain analyses, Pearson's correlation coefficient was used.	Poor concordance between COx and TFA methods to assess autoregulation (r = 0.21, p = 0.097). COx appears more robust than coherence and gain.
Caicedo 2014	*N* = 9 <32 weeks, first 3 days of life. 5 with IVH grade III-IV matched to 4 without (GA, BW, and gender). Clinical setting	MABP HR	INVOS 4100–5100: rSO_2, Sampling rate 1 Hz.	Relation between HR, MABP, and rSO_2	Median filter of seven samples. Artifacts removed. Using PRSA or BPRSA.	Nonlinear relationship between ABP and rSO_2 for both increasing (input signal increase) and decreasing (input signal decrease) anchor points. Especially in the patients with IVH, the time profiles of the PRSA curves showed impaired autoregulation.

(*Continued*)

Table 1. (Continued).

Author/ year of publication	Characteristics of patient cohorts (number of infants, GA, age at recording, and specific characteristics)	Input parameters (all using spontaneous fluctuations)	Output parameters (NIRS device and accompanying signal, sampling time/rate, and setup)	Definition for (impaired) autoregulation	Methods of measurement: -Duration of measurement -Duration of single epoch -Mathematical approach -Frequency band -% overlap	Clinical implication/main results; data interpretation by the authors
Eriksen 2014	$N = 60$[a] 26 ± 1 weeks Day 1 Clinical setting	MABP	NIRO-300: TOI, sampling rate 2 Hz Probe secured to the frontotemporal or frontoparietal region of the head with a flexible bandage.	A negative COx indicates an intact autoregulation, as a result of constriction of the cerebral arteries in response to increases in MABP.	2.3 h sampling. Moving linear correlation coefficient between 10-s samples of TOI and MABP, calculated with 10-min epoch with 1 min moving window. The mean of six COx values gave one COx for each 10-min epoch. One grand mean for each infant was calculated as a weighted mean, using the variability in MABP in 10-min epoch as weighting factor.	COx was not associated with GA, BW, CRIB score, and gender and not affected by treatment with antibiotics, development of IVH, or mortality. Higher COx in infants receiving saline bolus or surfactant. Only dopamine had significant negative influence COx in multivariate model: COx was 0.41 in the dopamine group and 0.08 in the group of infants not treated with dopamine ($p < 0.001$)
Mitra 2014	$N = 31$ 23–32 weeks 1–6 days All ventilated Clinical setting	MABP HR	NIRO200NX: TOI	Zero or negative TOx suggests intact autoregulation.	At least 2 h TOx (moving correlation coefficient between MABP and TOI) and TOHRx (see da Costa above)	Higher TOHRx related to higher CRIB score. TOHRx and CRIB: $r = 0.55$; $p = 0.0013$, FvHRx and CRIB: $r = 0.51$; $p = 0.0035$. Positive TOHRx related to more inotropic support, more PDA and more IVH.
Riera 2014	$N = 54$ 27 ± 2 weeks Day 1–2 Clinical setting	MABP, SVC flow	NIRO200NX: TOI Sampling rate 2 Hz Sensor placed at the frontoparietal level.	Threshold BiAR-COH of 0.58 and COH 0.52 identified low SVC flow.	9.5 h (mean) 30-min epochs (for COH 10 min segments with 50% overlap) at frequency 0.003–0.04 Hz (VLF). BiAR-COH. Coherence.	BiAR-COH associated with IVH grade 3–4 (OR 2.5, $p < 0.001$), mortality (OR 3.4, $p < 0.001$), and the need for hemodynamic support (OR 1.3, $p < 0.001$).
Verhagen 2014	$N = 25$ 25–31 weeks 2–64 h Clinical setting	MABP SpO_2	INVOS 4100–5100: rSO_2, FTOE One sample every 5 min Probe was placed on the left frontoparietal side of the infant's head and kept in place by an elastic bandage.	Negative Spearman correlation between FTOE and MABP suggests intact autoregulation.	24 h	No relation with clinical characteristics, including CRIB score, PVE, IVH, PDA, and mortality.
Alderliesten 2013	$N = 30$ infants with IVH vs. 60 without IVH 24–31 weeks 0–72 h Clinical setting	MABP	INVOS 4100–5100: rSO_2. Sampling rate 1 Hz. Probe was placed on the frontoparietal side of the infant's head and attached firmly with an elastic bandage.	Correlation between MABP and rSO_2, r value > 0.5 considered as impaired autoregulation.	Average of 10 × 1 min correlation within 24–36 h before IVH and within 24 h after IVH	More time with impaired autoregulation before (14% vs. 9%; $p < 0.01$) and after (15% vs. 9%; $p < 0.01$) IVH compared to controls.
Hahn 2012	$N = 60$[a] 27 ± 1 weeks Day 1 38% ventilated Clinical setting	ABP	NIRO-300: TOI 2 Hz Probes secured to the frontotemporal or frontoparietal region of the head with a flexible bandage.	TFA (coherence and gain) Coherence value >0.47 in the VLF range and >0.45 in the LF range.	2.3 ± 0.5 h 10-min epochs (3.5-min segments with 50% overlap) of VLF (0.003–0.04 Hz) and LF (0.04–0.1 Hz) bands.	No association between MABP, coherence, or gain with IVH or mortality. No association with inflammation (IL-6).

(*Continued*)

Table 1. (Continued).

Author/ year of publication	Characteristics of patient cohorts (number of infants, GA, age at recording, and specific characteristics)	Input parameters (all using spontaneous fluctuations)	Output parameters (NIRS device and accompanying signal, sampling time/rate, and setup)	Definition for (impaired) autoregulation	Methods of measurement: -Duration of measurement -Duration of single epoch -Mathematical approach -Frequency band -% overlap	Clinical implication/main results; data interpretation by the authors
Caicedo 2012	*N* = 18 25–29 weeks	MABP	NIRO 300: TOI 6 Hz	n.a.	2–4 h A comparison of various mathematical approaches: -Correlation coefficient -TFA coherence -Modified coherence -Transfer function gain -Variance-based analysis -Sensitivity analysis -Elementary effects approach	n.a.
Wong 2012	*N* = 32 <29 weeks 1–3 days All mechanically ventilated Clinical setting	MABP	NIRO 200: TOI 6 Hz The probes were placed over the temporoparietal region.	TFA (coherence and gain) High coherence values, possibly with a simultaneous high gain, suggests impaired autoregulation.	4–6 h/day 20-min epochs 0.003–0.02 Hz frequency band TFA	A high coherence and gain was associated with increased cerebral injury or death. Coherence also related to MABP variation (R^2 = 0.12–0.19, p = 0.03 and 0.01, on day 1 and 3, respectively)
Caicedo 2011 Adv Exp Med	*N* = 53 29 ± 2 weeks Clinical setting	MABP	INVOS 4100 and NIRO 300: rSO_2 and TOI 0.33 Hz (filtered)	Correlation or (partial) coherence coefficient: >0.5 considered as impaired autoregulation.	6–70 h 20-min epochs Correlation coefficient TFA (coherence) Partial coherence (Welch method): 10-min epochs with 75% overlap at the 0.003–0.1 Hz frequency band	Using correlation, the time with supposed impaired autoregulation related to CRIB score. No relation with outcome parameters (not specified by authors).
Caicedo 2011 Ped Res	*N* = 54 24–40 weeks Clinical setting	MABP	INVOS 4100 and NIRO 300: HbT and HbD vs. rSO_2 and TOI 0.33 Hz	n.a.	10–20-min epochs 75% overlap, at 0.0042–0.00837 Hz for 60s data and 0.0033–0.04 Hz for 3s data. Correlation and TFA coherence.	Correlation and coherence show little agreement within patients, especially during periods with limited MABP variability HbD and HbT seem less robust than rSO_2 or TOI, with similar scores.
Gilmore 2011	*N* = 23 26 ± 1 weeks 1–3 days All ventilated for at least some part of the recording Clinical setting	MABP	Foresight: rSO_2 0.5 Hz	Intact autoregulation defined as COx <0.5	0.6–4 days 5-min epochs Low-pass filtered. Moving correlation coefficient (COx), with 97% overlap.	Significant relationship between lower MABP and impaired autoregulation (r = 0.51, p = 0.013).
Zhang 2011	*N* = 17 24–29 weeks 1–3 h Clinical setting	MABP	NIRO 300: HbO_2, HHb, HbD, and TOI Synchronized converted data at 8 Hz	Relation with CRIB-II score and various cross-spectral TFA functions.	10 min artifact-free epoch, TFA (gain, phase, and coherence) according to Welch using 4-min epochs and 75% overlap. 0.02–0.04 Hz (VLF), 0.04–0.15 Hz (LF), and 0.15–0.25 Hz (MF) frequency bands.	Moderate correlation between CRIB score and MABP-HHb phase in the LF range and higher correlations between CRIB score and MABP-HHb coherence in LF range

(*Continued*)

Table 1. (Continued).

Author/ year of publication	Characteristics of patient cohorts (number of infants, GA, age at recording, and specific characteristics)	Input parameters (all using spontaneous fluctuations)	Output parameters (NIRS device and accompanying signal, sampling time/rate, and setup)	Definition for (impaired) autoregulation	Methods of measurement: -Duration of measurement -Duration of single epoch -Mathematical approach -Frequency band -% overlap	Clinical implication/main results; data interpretation by the authors
De Smet 2010	*N* = 30 Three sets of preterm infants from three different hospitals in clinical setting Approximately 28 ± 3	MABP	Critikon Cerebral Oximeter: HbD, INVOS4100: rSO_2, NIRO 300: TOI SpO_2	Correlation coefficient or TFA coherence >0.5 suggests impaired autoregulation.	10, 12.5, and 15-min epochs, 50% overlap. 0.0033–0.04 Hz frequency band. Correlation coefficient TFA (coherence) Partial coherence, for eliminating effect of fluctuating SpO_2	Partial coherence method appeared more accurate in predicting brain damage and more sensitive for detecting impaired autoregulation
Hahn 2010	*N* = 22 24–29 weeks 1 to 2 days 9% artificially ventilated Clinical setting	MABP	NIRO 300: TOI 2 Hz Probes secured to the frontotemporal or frontoparietal region of the head with a flexible bandage.	High coherence suggests impaired autoregulation.	1.2–3.7 h At 0.003–0.04 Hz and 0.04–0.1 Hz frequency bands. 10-min epochs, 50% overlap TFA (coherence)	Precision of autoregulation measurement can be improved by taking MABP variation into account.
De Smet 2009	*N* = 20 24–39 weeks 570–1470 g	MABP	NIRO-300: HbD and TOI 0.2 Hz	Higher concordance between HbD and MABP (new scoring system introduces for critical percentage of recording time) suggests impaired autoregulation.	1.5–23.5 h Correlation coefficient TFA (partial coherence)	TOI shows similar results compared to HbD as output parameter.
O'Leary 2009	*N* = 88 23–30 weeks First 5 days Clinical setting	MABP	NIRO-500: HbO_2, Hb, HbD 2 Hz	Higher gain and higher coherence indicate impaired autoregulation.	<12 h 10-min epochs at low- (0.05–0.25 Hz), medium- (0.25–0.5 Hz), and high- (0.5–1.0 Hz) frequency range. TFA (coherence and gain).	Higher gain was associated with increased risk of developing GMH/IVH or PVL, only in the low-frequency range (p = 0.03–0.05).
Wong 2008	*N* = 24 26 ± 2 weeks 28 ± 22 h Clinical setting	MABP	NIRO-300: TOI 1 Hz Probes are placed over the temporoparietal region of the infants head	Coherence value >0.5 and higher gain in the 0.003–0.1 Hz range suggest impaired autoregulation.	2–4 h 20-min epochs (five segments of 10 min with 75% successive segment overlap) at ULF (0.003–0 .02 Hz), VLF (0.02–0.05 Hz), and LF (0.05–0.1 Hz). TFA (coherence and gain)	Higher coherence and higher gain in the ULF range (0.003–0.03 Hz), were found in the sickest preterm infants, with strong correlation with CRIB score (r = 0.57, p < 0.01). No association between the averaged coherence and ultrasound cerebral abnormalities.
Soul 2007	*N* = 90 23–30 weeks First 5 days Clinical setting No preexisting major brain injury/ malformations or genetic syndromes	MABP	NIRO 500: HbO_2, Hb, HbD 2 Hz	Coherence values >0.77 suggest impaired autoregulation.	10-min epochs at LF range (0–0.04 Hz). TFA (coherence)	Impaired autoregulation is associated with low GA (p = 0.018), low BW (p = 0.038), and hypotension (r = 0.46, p < 0.0001), maternal hemodynamic factors (pregnancy-induced hypertension, hemorrhage during labor, and placental infarction).
Morren 2003	Several preterm infants, no further clinical information	ABP	NIRO 300: HbD 0.2 Hz	n.a.	30-min epochs 0–0.1-Hz frequency range Correlation coefficient TFA (coherence) A (near) linear model for assessment of common part for two signals (CPC).	Correlation and common part analyses seem more sensitive for parallel changes in ABP and HbD than coherence analysis.

(*Continued*)

Table 1. (Continued).

Author/ year of publication	Characteristics of patient cohorts (number of infants, GA, age at recording, and specific characteristics)	Input parameters (all using spontaneous fluctuations)	Output parameters (NIRS device and accompanying signal, sampling time/rate, and setup)	Definition for (impaired) autoregulation	Methods of measurement: -Duration of measurement -Duration of single epoch -Mathematical approach -Frequency band -% overlap	Clinical implication/main results; data interpretation by the authors
Tsuji 2000	*N* = 32 23–31 weeks First 3 days High risk for brain injury Clinical setting	MABP	NIRO 500: HbO_2, HHb, HbD 2 Hz Probe 1 cm above the supraorbital ridge with the transmitting optode 1 cm lateral to the midsagittal plane on either the right or the left forehead and the receiving optode 3 cm lateral to the transmitting optode.	Coherence value >0.5 suggests impaired autoregulation.	30-min epochs at ULF (0–0.01 Hz), VLF (0.01–0.05 Hz), and LF (0.05–0.1 Hz) frequency bands. TFA (coherence)	Higher coherence in the VLF range with grade 3–4 GMH-IVH or PVL. More severe ultrasound abnormalities when coherence was >0.5 somewhere in the first 3 days of life (47% versus 13%).

The six columns correspond to the six paragraphs 6.1 through 6.6.

ABP: arterial blood pressure; BPRSA: bivariate phase-rectified signal averaging; BiAR-COH: bivariate autoregressive spectral coherence; BW: birth weight; COH: coherence; CRIB score: clinical risk index for babies-score; COx: cerebral oximetry index; FTOE: fractional tissue oxygen extraction ($SpO_2 - rSO_2$)/SpO_2); GA: gestational age; Hb: hemoglobin; HbD = HbO_2 − HHb; HHb: deoxy-hemoblobin; HbO_2: oxygenated hemoglobin; HbT: total hemoglobin; HR: heart rate; IL: interleukin; IVH: intraventricular hemorrhage; LF: low frequency; MABP: mean arterial blood pressure; MDI: mental developmental index; MF: mid frequency; n.a.: not applicable; NIRS: near-infrared spectroscopy; O_2Hb: oxygenated hemoglobin; OI: oxygen index (O_2Hb − HHb/2); PDA: patent ductus arteriosus; PRSA: phase-rectified signal averaging; PVE: periventricular echodensities; PVL: periventricular leukomalacia; rSO_2: regional cerebral oxygen saturation; SpO_2: arterial oxygen saturation; StO_2: tissue oxygen saturation; SVC flow: superior vena cava flow; TFA: transfer function analysis; tHb: total hemoglobin; TOHRx: tissue oxygenation heart rate reactivity index; TOx: tissue oxygenation; TOI: tissue oxygenation index; VLF: very low frequency; ULF: ultralow frequency; OR: odds ratio; GMH/IVH: germinal matrix or intraventricular hemorrhage.

[a]Same population.

autoregulation at the bedside in 32 preterm infants less than 2 weeks of postnatal age [6]. They found higher coherence between MABP and NIRS-derived cerebral tissue levels of HbD in those infants that developed severe IVH or PVL. In the following years, others performed similar studies, mostly in the very preterm infants born before 32 weeks of gestation. Population size varied between 5 and 90 infants. Most measurements were done during the first 3 days of life, some up to 4 weeks after birth (Table 1).

6.1.2. Selection Bias

Using (M)ABP as the input parameter for autoregulation requires the presence of an indwelling arterial catheter. Inserting an arterial catheter for the purpose of studying autoregulation in this very small and vulnerable population is deemed unethical, and therefore, only infants with arterial catheters inserted for clinical reasons were included in these studies. This probably gives a selection bias of the sickest infants. On the other hand, the infants too small or technically challenging for insertion of an arterial catheter might have been excluded from the studies.

6.1.3. Clinical information

Most authors present baseline characteristics of the infants included, such as being artificially ventilated or not. Others focus on the techniques and hardly give any information on the infants included, which may hamper interpretation of data presented. Out of the 25 articles studied, 14 mention $PaCO_2$ as a possible confounder, of which 3 actually measured $PaCO_2$ and assessed the relationship between $PaCO_2$ and outcome [34,41,42] and 2 assessed the influence of $PaCO_2$ on cerebrovascular autoregulatory measures [29,56]. None found any relation between $PaCO_2$, outcome, and autoregulation status.

6.2. Cerebral perfusion pressure: ABP or HR?

6.2.1. Cerebral perfusion pressure

Until 2014, all studies used MABP as the input parameter for autoregulation calculations using NIRS. As ICP monitoring is not a standard of care in preterm infants, ABP is only available as the driving pressure for these calculations. The influence of ICP in adults, e.g. those with traumatic brain injury, is likely to significantly affect the CPP, while in preterm infants, it is fluctuations in the transitional circulation and systemic blood pressure which probably have a bigger effect on cerebral perfusion.

6.2.2. Shunting

Limitations of ABP measurements in preterm infants are the fact that ABP deriving from the ascending aorta may differ from the measured MABP due to shunting of blood typically for the preterm infants to and from the pulmonary artery over the ductus arteriosus, which branches just after the aortic arch. The influence of this shunt on MABP may be important as the fall in ABP from a large duct is due to the diastolic steel, while the systolic pressure is usually the same. Furthermore, blood flow towards the brain may be influenced by other factors that increase CBF at the expense of blood flow to the less vital organs for so-called 'brain-sparing' mechanism. This is especially important in intrauterine growth-restricted infants. This 'brain-sparing' phenomenon may continue after birth [44].

6.2.3. Spontaneous ABP fluctuations

To be able to use ABP for assessment of autoregulation, spontaneous variations in ABP are mandatory. Wong et al. studied MABP variability and cerebrovascular autoregulation. Impaired autoregulation was defined as a high coherence between fluctuations in MABP and the NIRS-derived TOI. They found impaired cerebrovascular autoregulation to be associated with increased MABP variability in most infants, but impaired autoregulation could also be found with decreased MABP variability in the sickest preterm infants [57]. Hahn et al. investigated whether the precision of the cerebrovascular autoregulation index coherence improved while adjusting for larger MABP fluctuations [58]. They studied 22 very preterm infants (GA <32 weeks) and adjusted for variability in ABP within and between the repeated measurements. They found that the within measurements, repeatability or precision of the autoregulation calculations improved while adjusting for the magnitude of ABP fluctuations.

6.2.4. Heart rate

A new approach to the assessment of cerebrovascular autoregulation in preterm infants was presented by Mitra et al. Instead of ABP, the heart rate (HR), derived from noninvasive ECG monitoring, was chosen as the input variable for the cerebrovascular reactivity challenge [59]. The tissue oxygenation HR reactivity index (TOHRx) was introduced and calculated in a similar manner to previously described autoregulatory indices such as the TCD-derived mean flow velocity index (Mx) and NIRS-derived TOx (cerebral oximetry index [Cox]) (Figure 2). TOHRx correlated significantly with the CRIB-II score in 31 preterm infants (GA <32 weeks), whereas the other indices did not. A trend in association between mortality and TOHRx was found. A trend for higher TOHRx values was seen in preterm infants who received inotropic treatment, had a hemodynamically significant PDA, or developed major IVH (grade 3–4) [59].

6.3. NIRS devices and their accompanying parameters

Before NIRS-based cerebral oximetry measurements of TOI/rSO_2 were developed, NIRS parameters used for the assessment of CBF changes were measurements of changes in cerebral HbT, HbO_2, and HbD levels. These parameters are sensitive to movement artifacts, which potentially limits their applicability in both research and clinical settings. This is less an issue for the NIRS parameters TOI or rSO_2, representing regional oxygenation as a relative measure of the percentage of the local oxygenated Hb in total Hb using published [61] or non-disclosed (manufacturer) calculation algorithms. Nevertheless, De Smet et al. showed in 2009 no difference between the use of HbD or TOI for autoregulation assessment [62]. Also, Caicedo et al. showed no relevant differences using HbD or HbT versus TOI or rSO_2 in the resulting correlation or coherence values, concluding that TOI or rSO_2 can also be used to study cerebrovascular autoregulation in preterm-born newborns [63]. TOI and rSO_2 parameters are most often used nowadays for autoregulation measurements.

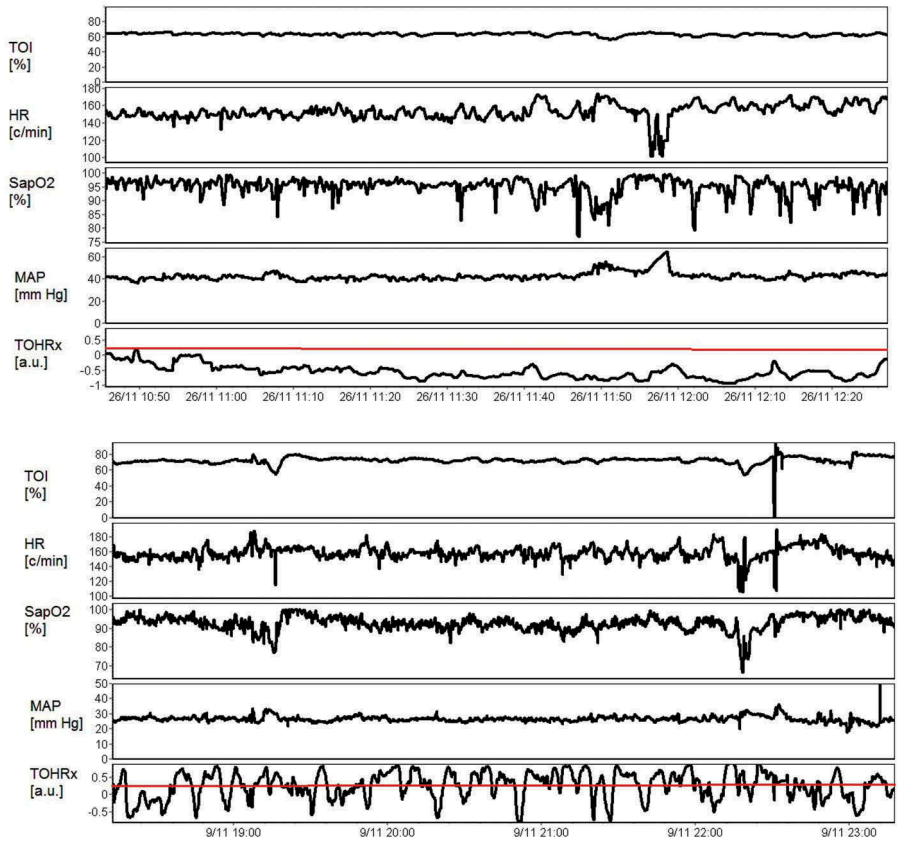

Figure 2. Recording of two preterm babies which one had permanently good autoregulation (negative TOHRx-mean −0.35; upper panel) and disturbed autoregulation(mostly positive TOHRX, mean 0.35- lower panel).Red line depicts elusive demarcation between working and disturbed autoregulation (0.25). TOI-tissue oxygenation index, HR- heart rate, SapO2- arterial saturation, MAP- mean arterial pressure, TOHRx- autoregulation index. X -axis: time scale. Based on clinical material described by Da Costa et al. [60]. Full color available online.

6.4. Definitions for impaired cerebrovascular autoregulation

Impaired cerebrovascular autoregulation is defined by a CPP-dependent CBF [8]. This relationship may be assessed in the time (correlation analysis) or frequency domain (transfer function analysis [TFA] with coherence, phase, and gain parameters). As an example, a higher correlation coefficient or coherence value between the input (e.g. CPP or MABP) and output parameters (CBF or TOI or rSO_2) might suggest impaired autoregulation.

6.4.1. Thresholds for coherence

Whether sufficient coherence is a prerequisite for reliable autoregulation calculation using gain and TFA or coherence has value on its own for assessing autoregulation is still a matter of debate [64]. Despite this, the coherence variable itself is frequently used to describe autoregulation status in preterm infants. Some authors have proposed an absolute threshold of coherence values for autoregulation impairment, which ranges in the literature from any value larger than 0 to coherence values of >0.77 [65]. Coherence >0.5 is the most frequently chosen threshold based on adult literature [66] or animal studies [67].

Tsuji et al. supported their choice using a cutoff value of 0.5 on the fact that more severe cerebral ultrasound abnormalities were seen in preterm infants with coherence values >0.5 during the first 3 days after birth (47%) compared with preterm infants with coherence scores <0.5 (13%) [6]. Hahn et al. mathematically calculated coherence thresholds for various MABP levels, using complex mathematical Monte Carlo simulations, resulting in coherence scores for autoregulation impairment to be >0.47 in the very-low-frequency range and >0.45 in the low-frequency range [58]. Riera et al. measured superior vena cave (SVC) flow and found that infants with coherence values between MABP and TOI >0.52 had lower SVC flow [37]. A possible explanation to this finding may be that below the lower ABP threshold for autoregulation, a reduced CBF and subsequently reduced SVC flow occur [68].

6.5. Methods of measurements

Of the 25 articles included in the table, 7 used time-domain analyses, 9 used frequency-domain analyses, 7 compared the two, and 2 used other techniques for the assessment of cerebrovascular autoregulation.

6.5.1. Time-domain analysis

Steiner et al. extended the use of NIRS parameters for dynamic cerebrovascular autoregulation assessment in adult intensive care patients at the bedside [69]. They calculated an index of autoregulation in the time domain using correlation coefficients between TOI and MABP (TOx), similar to other pressure reactivity parameters, Mx (using TCD) and pressure reactivity index (PRx, using ICP) [17]. Using continuous TOI and MABP monitoring, dynamic autoregulation indices like TOx can be

calculated continuously with simple moving correlation statistics. A positive TOx value might indicate an MABP-dependent cerebral oxygenation and CBF. The authors found a high correlation between the Mx index and TOx index in 23 adult patients with sepsis or septic shock, suggesting that both techniques probably contain comparable information about autoregulation [69].

In 2011, Gilmore et al. introduced the term COx in a preterm population, which is essentially the same as the TOx index, but using rSO_2 as a measure of cerebral oxygenation [30]. A cutoff value of 0.5 was used to delineate intact from impaired states of cerebrovascular autoregulation in 23 preterm infants (GA <30 weeks) with invasive MABP monitoring. Subsequently, COx values were grouped and averaged according to the average MABP in 5 mmHg bins, in order to delineate a range of MABP that is associated with intact cerebrovascular autoregulation (COx value near 0) or impaired cerebrovascular autoregulation (COx value near 1). Indeed, increased COx values occurred at lower MABP values, and lower MABP values were associated with longer periods of impaired cerebrovascular autoregulation (COx values >0.5). Preterm infants born with a lower GA had lower MABP values but unexpectedly did not show an increased duration with impaired cerebrovascular autoregulation [30]. Thirteen studies have used the TOx or COx technique for cerebrovascular autoregulation assessment in preterm infants (Table 1). Measurement length varied between 5 and 30 min, and in case of application of moving calculation windows, the overlap was most often set at 50–75%.

Some groups have used single correlations between low-frequency sampled MABP data (e.g. data averaged every hour) over longer measurement periods (i.e. 24 h) for cerebrovascular autoregulation assessment in preterm infants [40,42,56]. This is probably a rather rough method that may both overestimate and underestimate the infant's ability to adapt its arterioles to changes in ABP. It does not take variation of this cerebrovascular autoregulation ability in individual infants within the period measured into account. Nevertheless, in situations where there is a lack of sufficient data-points, or the technical ability to assess moving window coherence and transfer function, this method may roughly indicate the overall autoregulatory capacity of infants over a certain period of time.

6.5.2. Frequency-domain analysis

In total, 16 studies used frequency-domain analyses to study autoregulation in preterm infants (Table 1). Wong et al. assessed dynamic cerebrovascular autoregulation in the frequency domain, in 24 very preterm infants (GA <32 weeks). They employed a moving window of frequency-specific MABP and TOI measurements using TFA [34] (Figure 3). They computed 'power spectral densities' from the frequency-domain data, which were used to generate the TFA variables coherence and gain from the two signals. High coherence and increased gain values are interpreted as impaired dynamic autoregulation [16]. The authors state that the coherence function characterizes the frequency-dependent linear relation between MABP and TOI which is a prerequisite for reliable calculation of the gain using TFA. The gain represents the magnitude (or dampening effect) of changes in TOI (output signal) resulting from the change in MABP (input signal) at specific frequencies. Hahn et al. validated the use of the TFA variables coherence and gain from the two parameters TOI and MABP to assess cerebrovascular autoregulation in a piglet model [70]. For a detailed overview regarding the TFA analysis, we refer to the recent paper by Claassen et al. [71].

6.5.3. Frequency ranges for autoregulation calculation

The current pressure autoregulation concept is built on the fact that slow and prolonged periods of hypotension or hypertension are likely more injurious than fast and transient (beat to beat) changes in ABP. This concept is often referred to as the 'high-pass filter' principle of autoregulation [16]. Especially, the low- and the very-low-frequency ranges are considered physiologically most important for cerebrovascular autoregulation, since in these frequencies most adaptations of cerebral perfusion to slow ABP fluctuations are seen. However, in the very-low-frequency range, contributions of other physiological variables (like $PaCO_2$ and sympathetic influence) take place, making interpretation of cerebrovascular autoregulation results more complex [72]. TFA values can be calculated in different frequency ranges: 0.005–0.02 Hz (sub-very low frequency), 0.02–0.07 Hz (very low frequency), 0.07–0.15 Hz (low frequency), and 0.15–0.40 Hz (high frequency) [73], although various authors use various definitions for the various ranges. Tsuji et al. found a higher coherence score in the very-low-frequency range for preterm infants with severe cerebral ultrasound abnormalities (grade 3–4 GMH-IVH or PVL) compared to infants with normal or minimal abnormal ultrasound findings [6]. Also, Wong et al. showed highest coherence and gain in the very-low-frequency range (0.003–0.02 Hz) [34].

6.5.4. Time-domain versus frequency-domain analysis

Caicedo et al. compared various approaches for cerebrovascular autoregulation assessment. Based on measurements in 18 preterm infants, they calculated the time-domain Pearson correlation coefficient (COx) and the frequency-domain TFA (modified) coherence, gain, and phase [74]. The variable phase describes the phase shift or delay between the input and output signals. Higher gains and low-phase values probably represent impaired autoregulation. In addition, they investigated whether mathematical parameters used in the TFA such as measurement lengths (epoch length) and overlapping percentages influenced the final results. Maximal sensitivity for the assessment of autoregulation and power for the various approaches was reached at approximately 60% time-window overlap and using measurement length between 14 and 22 min. The authors found that the TFA gain and the Pearson correlation were the most robust methods to detect changes in the parameters compared to other methods such as TFA phase and coherence. However, correlation ignores any delays in the signals under analysis, while TFA can assess causal relationship between MABP and CBF [74]. Morren et al. suggested that because time-domain correlation showed a higher concordance between HbD and MABP in several preterm infants (number not specified) than TFA coherence did in those infants, the correlation index might be a more sensitive measure for impaired autoregulation than coherence [75].

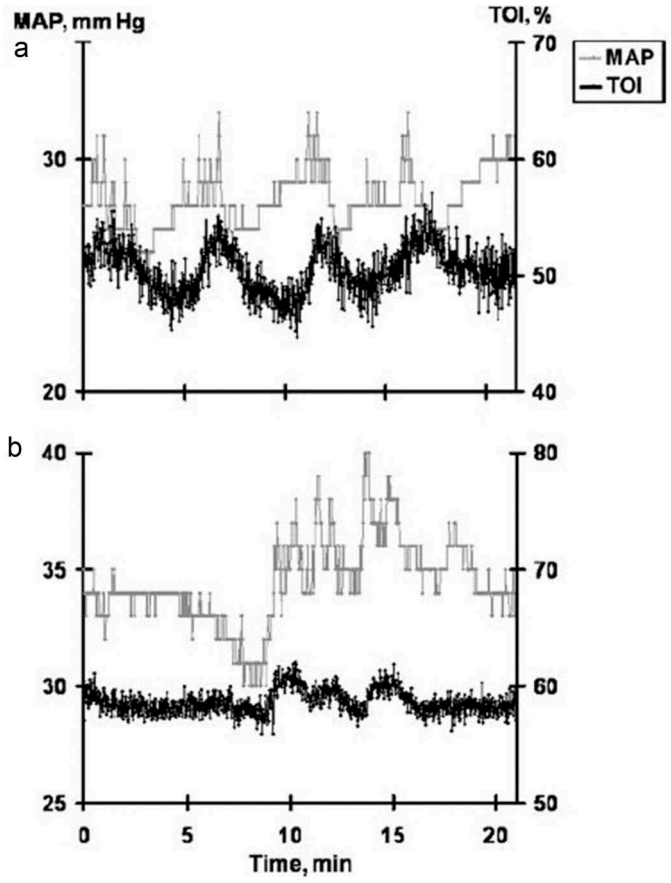

Figure 3. Example of high TFA for TOI and MAP values in the ultralow frequency from the Wong et al. study in 2 preterm born infants born at 23 and 25 weeks gestation, shown respectively in (a) and (b) [34]. The infant in (a) showed fluctuations of TOI of higher magnitude in response to changes in MAP, compared with the infant in (b). Accordingly, the value of gain in the ULF range for the recording in (a) was higher than the value for the recording in (b) (0.8 vs 0.4%/mm Hg, respectively). Note that both recordings showed concordant changes between MAP and TOI waveforms, with the ULF coherence values both at 0.6. Reproduced with permission from Pediatrics, Vol. 121, Page(s) e604-11, Copyright © 2008 by the AAP. Abbreviations: TOI; tissue oxygenation index, MAP; mean arterial pressure, ULG; ultra-low frequency.

Eriksen et al. also compared the time- versus frequency-domain methods for describing cerebrovascular autoregulation. In the frequency-domain analysis, they used the variables coherence and gain, and for the time-domain analysis, they used COx in 60 very preterm infants (GA 26.6 ± 1.3 weeks). They found that the concordance between the two methods was poor: the two methods did not classify the same infants as having intact or impaired cerebrovascular autoregulation [76].

De Smet et al. suggested that the partial coherence (PCOH) method might be more accurate in predicting brain damage and more sensitive for detecting impaired autoregulation [77]. PCOH allows for the elimination of the linear influence of one signal on another and can therefore be applied in periods of fluctuating peripheral arterial saturation (SaO_2). In a cohort of 30 preterm infants, using PCOH, they found longer periods of time and more patients with pressure-passive NIRS values, independent of SaO_2, than using the simple coherence value.

Comparing all these studies do not reveal any clear benefit of any of the mathematical approaches, and the different methods provide different results on the autoregulatory capacity of preterm infants. Without a gold standard for measuring cerebrovascular autoregulation, it may be impossible to prove any of the methods optimal. In addition, the heterogeneous mathematical approaches and outcome measurements hamper comparison between neonatal studies on autoregulatory capacity.

6.5.5. Other autoregulation models

Riera et al. proposed that the assumed synchronized changes in the input and output parameters representing CPP and CBF such as those described above undermine any other possible time relationship between the two. They therefore introduced a new prediction model, the bivariate autoregressive spectral coherence (BiAR-COH) method, to predict cerebral oxygenation changes in relationship to MABP changes from previous samples in the very-low-frequency range. They showed that this model was superior to the simple TFA coherence method for predicting low SVC flow or adverse outcome in 54 preterm infants [37].

Bauer et al. suggested a methodological solution for the fact that many input oscillations are quasiperiodic, nonstationary, and noisy [60]. They propose a phase-rectified signal averaging (PRSA) method, which uses anchor points in the input signal which are used to align the oscillatory systolic ABP fluctuations, followed by a signal averaging. Benefit of PRSA over conventional frequency analysis and correlation analysis is the fact that in noisy or quasiperiodic signals, phase changes may lead to over- or underdetection of correspondence between signals. Using PRSA, anchor points are determined from the input signal itself, searching for phase-synchronized signals. Caicedo et al. also reported on the clinical capacity of (bivariate) PRSA to differentiate between five preterm infants with high-grade IVH versus four control infants with normal cranial ultrasound findings, matched by GA, BW, and sex [78]. They used both ABP (one mean ABP and one systolic ABP) and HR combined with rSO_2 measurements for their analyses. The results showed the presence of a nonlinear relationship between ABP and rSO_2 for both increasing (input signal increase) and decreasing (input signal decrease) anchor points. Especially in the patients with IVH, the time profiles of the PRSA curves showed impaired autoregulation possibly due to a difference in maturation compared to control infants with matched GA. The authors suggest that larger studies are warranted to validate bivariate PRSA analyses for cerebrovascular autoregulation assessment in preterm infants.

6.6. Clinical implications for autoregulation measurements

6.6.1. Clinical end points

Many authors have used clinical outcome such as IVH or mortality to validate their autoregulation measurements, assuming IVH and mortality to occur more often with impaired autoregulation (Table 1). These relationships may not be causal, especially with the lack of a gold standard for assessing cerebrovascular autoregulation. Noteworthy, not all studies found a positive relation between impaired autoregulation and chosen clinical end points [56,79,80], where many others did [6,29,34,37,41,59,77,78,81–83]. In contrast to all others, Stammwitz et al. even found a positive relation between *low*

coherence and IVH development in 31 ventilated preterm infants with RDS. The authors suggest that within the frequency range they measured (0–0.01 Hz and 0–0.1 Hz) that a high coherence is a reflection of 'a high coordination of physiological cycles and an indicator of maturation and integrity' [84].

For quantifying the time burden of limited autoregulatory capacity in preterm infants, Soul et al. introduced the term 'pressure-passive index' (PPI) [29]. This PPI is defined as the percentage of 10-min periods with high coherence (>0.77) in the very-low-frequency range between MABP and NIRS-derived HbD values. This occurred in the majority of infants for mean 20% of the time and was significantly associated with low GA and BW, hypotension, and maternal hemodynamic factors. In the study by Wong et al., a high coherence and high gain was found especially in the sickest preterm infants [34]. Coherence was superior in predicting mortality to the CRIB score, a highly predictive index of mortality [85,86]. However, in contrary to what Tsuji et al. [6] had previously found, no association was found between the averaged coherence and ultrasound cerebral abnormalities. This study was probably underpowered to find such associations [34].

6.6.2. Using the integrity of autoregulation to define optimal blood pressure

Many preterm infants are probably able to regulate CBF within certain limits of ABP. An objective measure of 'optimal' ABP could be the strength and objective of assessing cerebrovascular autoregulation or reactivity. This has been extensively investigated in adult patients [87]. Using TOHRx as an index of cerebrovascular reactivity in a cohort of 60 preterm infants, da Costa et al. were able to define ABPopt in 81% of the infants using a moving 4-h monitoring window (Figure 4). They showed (Figure 4) that deviation from ABPopt correlated with IVH (MABP > ABPopt) or with mortality (MABP < ABPopt) [82]. The ABPopt methodology could provide clinicians with a 'safe' range of MABP in the individual patient at any specific time point and then to adjust treatments to keep MABP within that range; however, the data need to be available in real time, and this approach would then need formal prospective testing.

7. Conclusion and future directions

For understanding and improving the long-term neurodevelopmental outcome of preterm infants, it might be crucial to be able to adequately and safely assess the autoregulatory capacity and to detect and prevent unnoticed cerebral hypo- or hyperperfusion and secondary brain injury. NIRS might fulfill these requirements and can be used to measure regional cerebral oxygenation as a surrogate for changes in regional CBF.

Although the methodology has progressed over time, uncertainties regarding the interpretation of the absolute signals and autoregulation calculations algorithms remain, limiting its current clinical applications at the moment. Many different NIRS parameters and cerebrovascular autoregulation calculations are currently being used for the assessment of cerebrovascular autoregulation in preterm infants (Table 1). Also, newly developed techniques that are based on the NIRS principle such as diffuse correlation spectroscopy [88,89] may offer novel opportunities for the assessment of CBF and autoregulation in preterm infants.

As we show in this overview, the variety in methodology makes understanding and interpretation of the results for clinicians difficult. At the moment, there is a large variety of mathematical approaches, measurement lengths, overlap percentages, frequency ranges, and signal (pre-)processing. In studies on preterm infants, most authors have used correlation indices (time domain) or TFA (frequency domain) to describe the linear relationship between MABP and NIRS estimates of CBF. Most studies agree on the fact that these approaches indeed assess cerebrovascular autoregulation which often is related to short-term cerebral injury.

In adult research, steps have been taken very recently to standardize the autoregulation measurements and

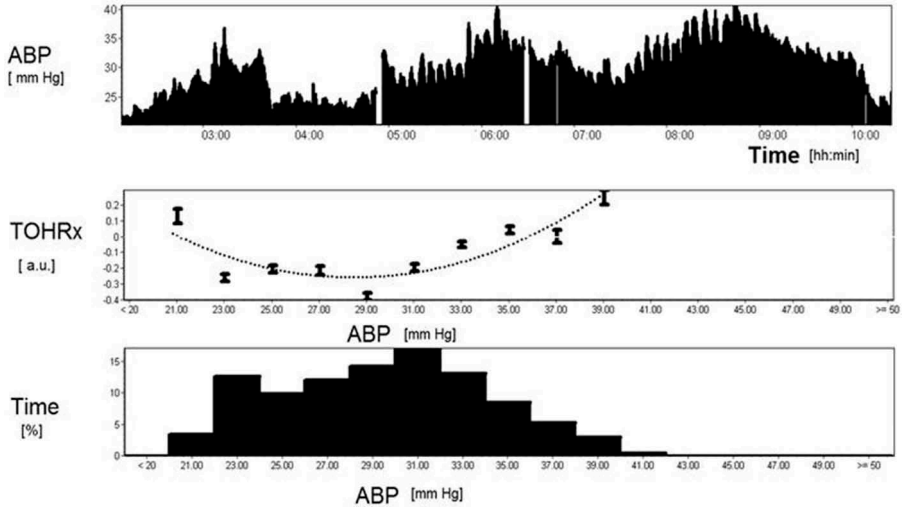

Figure 4. Example of determination of ABP_{opt} (in this cases minimum of the U-shape curve suggest 'optimum' at ABP = 29 mm Hg) using clinical data previously published by Da Costa et al. [60] (with permission from the authors). Abbreviations: ABP; arterial blood pressure, TOHRx; tissue oxygenation heart rate reactivity index.

methodology for TCD measurements [71]. Such initiatives have not been undertaken for NIRS.

For clinical purposes, NIRS-based autoregulation assessment may help in defining the 'optimal ABP' or the lower level of autoregulation for an individual infant, which might provide important information for clinicians to manage ABP in a patient-specific manner. However, the need for continuous ABP measurement implies the presence of an indwelling arterial line, which is not always available in these small preterm infants. It would therefore be interesting to better understand the role of HR in cerebrovascular reactivity, as this measurement is universally available in all infants on NICU.

Finding the optimal way to validly assess cerebrovascular autoregulation in preterm infants in a clinical setting would allow for clinicians to guide treatment and improve outcome in this vulnerable population. In our opinion, steps should be taken towards agreement on uniform methodology with the aim of using indices of cerebrovascular autoregulation as a marker to optimize blood pressure management and cerebral perfusion in preterm infants. This should then be investigated in large trials with meaningful clinical outcomes.

8. Expert commentary

Management of CPP in preterm-born infants is challenging due to largely unknown individual targets and maturation status of cerebrovascular autoregulating vessels. One attractive option is to estimate ABP targets for providing adequate CPP and CBF, by assessing the dynamic autoregulatory capacity at the bedside continuously and noninvasively. NIRS might fulfill these requirements and can be used to measure regional cerebral oxygenation as a surrogate for changes in regional CBF. Autoregulation research in preterm infants has reported many methods for measuring autoregulation using different mathematical models, signal (pre)processing, and data requirements (frequency bands, measurement length, and data overlap percentages). Methodological comparative studies are limited. A gold standard for validation of the measurement methods is lacking, and different clinical outcome variables for validation have been used. At present, it remains unclear which NIRS signals and (manufacturer) algorithms should be used that result in the most accurate and clinically relevant assessment of cerebrovascular autoregulation. Future studies should focus on optimizing strategies for cerebrovascular autoregulation assessment in preterm infants in order to develop autoregulation-based cerebral perfusion treatment strategies.

9. Five-year view

Prerequisite for incorporating autoregulation measures in clinical decision-making would be to investigate which of the available NIRS devices, parameters, and algorithms have the highest and most reliable diagnostic value for regional cerebral oxygenation changes. However, the only way to validate the bedside NIRS measurement is the use of clinical outcome as a surrogate of abnormal cerebral perfusion, since no gold standard for measurements of cerebral hypo- or hyperperfusion in human preterm infants exists. Alternatives for invasive ABP measurements as a surrogate for CPP also need to be explored. There are several reasons; first, ABP in the preterm may not represent CPP, and second, not all preterm infants have indwelling arterial lines for continuous ABP measurements. Thirdly, as fluctuations in the input signal are essential for challenging the autoregulation system, the use of (noninvasive) HR-based cerebrovascular reactivity deserves further exploration. Consensus should be reached about the selection of most relevant clinical outcome variables for comparing the diagnostic and prognostic value of different NIRS methods. Standardization of the methodology should be advocated and published.

The next step would be to design intervention studies on implementing knowledge on autoregulatory capacity to see if various clinical interventions indeed improve physiological end points like cerebral oxygenation and autoregulatory capacity. Finally, this should lead to the development of phase III studies, for example, comparing cerebrovascular autoregulation-defined optimal ABP management with conventional ABP management, with important clinical end points such as long-term neurological outcome.

Key issues

- Cerebrovascular autoregulation is a complex process that is influenced by many different factors in preterm infants. The level of maturity and function of the preterm cerebral arterioles remain a matter of debate.
- There is a promising role for cerebrovascular autoregulation measurement using NIRS in preterm infants due to its noninvasive, cheap, safe and continuous signals.
- Cerebrovascular autoregulation in preterm infants has been quantified in various ways, using different input and output parameters, and various mathematical approaches, without clear standardization or validation.
- Most authors have used correlations (time domain) or transfer function (frequency domain) analysis to describe the relationship between ABP and NIRS. There is no agreement regarding measurement length, data overlap percentage, which frequency bands contain the most relevant information and how to combine NIRS with other brain monitoring signals.
- Since the heart rate (HR) signal shows more slow spontaneous fluctuations compared to the ABP signal in preterm infants, and can be assesses non-invasively, the use of HR based cerebrovascular reactivity indices deserve further exploration.
- In this review we provide an overview of the different NIRS methodologies used for assessing preterm cerebrovascular autoregulation, and their (mostly observational) data collection and interpretation. At present the large diversity and heterogeneity of the NIRS studies limits conclusions about the (possible) clinical benefit of autoregulation monitoring with NIRS.

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