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Cerebral autoregulation in the preterm newborn using near-infrared spectroscopy: a comparison of time-domain and frequency-domain analyses

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Abstract. The aim was to compare two conventional methods used to describe cerebral autoregulation (CA): frequency-domain analysis and time-domain analysis. We measured cerebral oxygenation (as a surrogate for cerebral blood flow) and mean arterial blood pressure (MAP) in 60 preterm infants. In the frequency domain, outcome variables were coherence and gain, whereas the cerebral oximetry index (COx) and the regression coefficient were the outcome variables in the time domain. Correlation between coherence and COx was poor. The disagreement between the two methods was due to the MAP and cerebral oxygenation signals being in counterphase in three cases. High gain and high coherence may arise spuriously when cerebral oxygenation decreases as MAP increases; hence, time-domain analysis appears to be a more robust—and simpler—method to describe CA. © The Authors. Published by SPIE under a Creative Commons Attribution 3.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: [10.1117/1.JBO.20.3.037009](https://doi.org/10.1117/1.JBO.20.3.037009)]

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1 Introduction

Cerebral autoregulation (CA) is a mechanism that ensures a fairly constant cerebral blood flow (CBF) despite fluctuations in mean arterial blood pressure (MAP). Impaired CA has been associated with increased morbidity and mortality in neonates.^{1,2} Therefore, it is highly relevant to be able to measure a robust estimate of CA. In vulnerable patients, such as infants admitted to the Neonatal Intensive Care Unit, methods to estimate CBF noninvasively and continuously are preferable. Near-infrared spectroscopy (NIRS) offers this.

CA is described by the relationship between corresponding changes in MAP and CBF. Traditionally, two methods have been used to describe this relationship: frequency-domain analysis and time-domain analysis.

In the frequency domain, outcome variables are coherence and gain; the correlation and the regression coefficients are the outcome variables in the time domain. Coherence and the correlation coefficient describe the presence or absence of CA. However, CA is not an all-or-none phenomenon.^{3,4} Therefore, it is relevant to quantify the degree of impaired CA, i.e., to what extent (degree) changes in MAP are transferred to the cerebral circulation. Gain and the regression coefficient provide this information. There is, however, no agreement as to which method describes CA the best or whether the two methods are equivalent.

The aim of this study was to compare the two methods of describing CA: frequency-domain analysis and time-domain analysis.

2 Method

2.1 Data Recording

MAP was measured using a transducer connected to the arterial line. We used NIRS (NIRO 300 oxygenation monitor, Hamamatsu Photonics, Hamamatsu City, Japan) to continuously measure changes in the relative concentrations of oxygenated and deoxygenated hemoglobin. The oxygenation index (OI) is the difference between oxygenated and deoxygenated hemoglobin divided by a factor of 2. Changes in OI have previously been validated to represent changes in CBF, assuming that the oxygen metabolism remains constant during the measurements.^{5–7} The NIRS probes were fixed in a nontransparent probe holder (inter-optode distance = 4 cm) and secured to the frontotemporal or frontoparietal region of the head with a flexible bandage. NIRS, MAP, and SaO₂ (assessed by pulse oximetry) were sampled simultaneously at 2 Hz. Recordings were automatically stopped if changes in SaO₂ increased more than 5%. In case of disruption of signals, e.g., x-ray, manipulation of the infant, and blood gas sampling, measurements were interrupted. The data were automatically divided into 10-min epochs of uninterrupted recordings (median 10 epochs, range 4 to 17). The mean duration of measurement was 2.3 ± 0.5 h. Data from epochs containing obvious artifacts were deleted manually. In two epochs, short artifacts of the MAP signal (loss of signal was 7.5 and 15.5 s, respectively) were bridged by linear interpolation. In these two epochs, the surrounding data points were of similar magnitude.

2.2 Patients

We monitored 60 extremely and very preterm infants (mean gestational age: 26.6 ± 1.3 weeks) in their first day of life

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(mean postnatal age: 18 ± 9.4 h). During measurement, 23 infants (38%) were treated with mechanical ventilation, while the rest were treated with nasal continuous positive pressure.

2.3 Calculation of Cerebral Autoregulation

The primary analysis of these data has been published previously.⁸ In the previous study, CA was analyzed in the frequency domain. In the present study, data were reanalyzed in the time domain for comparison.

2.3.1 Time-domain analysis

The time-domain analysis is a statistical measurement of the linear dependency between OI and MAP. The OI and MAP signals were resampled in 10 s means (0.1 Hz). Using 10 s means corresponds to using a filter that filters out variations caused by pulsation and respiration. Cerebral oximetry index (COx) corresponds to Pearson's r in the correlation analysis and was introduced by Brady et al.⁹ COx was calculated for periods of 5 min with a 1-min sliding window; this time period for performing the analysis has previously been validated.⁹ The mean of the six COx values for each 10-min epoch gave one epoch mean COx value. To calculate one COx value for each infant, the epochs mean COx was adjusted for variability in MAP in the epoch. Here, the most weight was given to COx values calculated from epochs with high MAP variability. COx values can assume both positive and negative values. The more positive the COx, the more impaired the CA. Negative values can be seen when increased MAP leads to decreased OI as a consequence of vasoconstriction resulting in decreased arterial-venous ratio, i.e., intact CA. To quantify the degree of impaired CA, the averaged regression coefficient was calculated for each epoch in the same manner as COx. Like COx, the regression coefficient was weighted according to MAP variability to achieve one regression value for each infant.

2.3.2 Frequency-domain analysis

The frequency-domain analysis was introduced by Giller in an attempt to evaluate CA as a dynamic process by viewing CA as a system characterized by the relation between an input signal and an output signal, i.e., MAP and an estimate of CBF.¹⁰ A coherence analysis is a correlation in the frequency domain that describes the strength of the relation between OI and MAP at a particular frequency range. Coherence values are absolute and ranges between 0 and 1, with 0 indicating an intact CA (no correlation between MAP and OI) and 1 indicating the complete absence of CA (perfect correlation between MAP and OI). Gain is determined by the transfer function analysis and quantifies the extent to which a waveform is transferred from an input signal, i.e., MAP, to an output signal, i.e., OI. A reduced gain indicates that the output signal is damped and suggests an intact CA; a high gain reflects a high CBF variability in proportion to MAP variability.

Our analysis was performed for the frequencies in the very low-frequency range (0.003 to 0.04 Hz), corresponding to changes occurring over 25 to 300 s, which is the same time range that is used for the time-domain analysis. Three 5-min segments with 50% overlap were calculated for each 10-min epoch. Signals of OI and MAP were detrended and transformed into power spectral density by Fourier transform.⁴ The coherence and gain were averaged over the entire frequency band

for each 10-min epoch. For both coherence and gain, we calculated a weighted mean where MAP variability within each epoch was used as the weighting factor,¹¹ i.e., in each infant, epochs with high MAP variability were weighted in favor of those with a low MAP invariability. In this way, we ended up with a single value of coherence and gain in each infant.

2.4 Statistics

We performed an ANOVA to compare the variation within subjects (the test-retest variability) with the variation among subjects (population variation). This can be considered a measure of internal consistency or relative repeatability. To describe the relation between time- and frequency-domain analyses, Pearson's correlation coefficient was used. A Chi²-test was performed to determine the consistency between the classification of CA as normal or impaired using conventional thresholds [Cox ≥ 0.4 (Ref. 12) and coherence ≥ 0.5 (Ref. 11)]. A two-sided p -value below 0.05 was considered significant.

3 Results

3.1 Methods' Repeatability

Both the frequency- and time-domain analyses were able to discriminate between subjects at a highly statistically significant level, indicating a high relative repeatability of both methods (Table 1). However, the F -value for COx was higher than for coherence, whereas gain had significantly higher F -values compared with the regression coefficient. When the three most extreme cases, in which gain was high while the regression coefficient of the time-domain analysis was negative [marked on Fig. 2(b)], were excluded from the ANOVA analysis, the F -values of gain and the regression coefficient were comparable.

3.2 Signal Analysis

Both methods describe the relation between two signals, OI and MAP. If CA is impaired, then OI follows changes in MAP [Fig. 1(a)]. In contrast, if CA is intact, fluctuations in MAP do not change the OI signal [Fig. 1(b)], or MAP and OI signals might even be oppositely directed [Fig. 1(c)] as a result of vasoconstriction in response to increased MAP.

3.2.1 Comparison between coherence and cerebral oximetry index

The correlation between coherence and COx was weak ($r = 0.215$, $p = 0.097$) [Fig. 2(a)]. Accordingly, the infants classified as having impaired CA were not the same ($\text{Chi}^2 = 3.78$, $p = 0.052$).

3.2.2 Comparison between gain and regression coefficient

The correlation between gain and the regression coefficient was also weak ($r = -0.206$, $p = 0.115$) [Fig. 2(b)]. The unexpected negative correlation between the two methods was mainly due to three extreme cases. If we excluded these three cases, the correlation became positive ($r = 0.245$, $p = 0.066$), but still weak.

4 Discussion

The main finding of this study was that the concordance between the two methods used to estimate CA was poor: the

Table 1 Relative repeatability of the outcome variables, ANOVA ($N = 60$).

		Sum of squares (all cases)	Mean squares (all cases)	F (all cases)	F (The three most extreme cases excluded)	p -value
Coherence	Between subjects	2.299	0.039	3.36	3.37	<0.001
	Within subjects	6.525	0.012			
	Total	8.824				
COx	Between subjects	41.743	0.708	8.82	7.81	<0.001
	Within subjects	45.082	0.080			
	Total	86.825				
Gain	Between subjects	7.047	0.119	14.03	7.91	<0.001
	Within subjects	4.784	0.009			
	Total	11.831				
Regression coefficient	Between subjects	13.019	0.221	7.75	6.16	<0.001
	Within subjects	15.993	0.028			
	Total	29.012				

two methods did not classify the same infants as having intact CA. Furthermore, in three extreme cases, a high gain was associated with a negative regression coefficient.

4.1 Does It Matter Which Method We Choose When Estimating Cerebral Autoregulation?

In the literature, two mathematical methods dominate the way of describing CA in infants with spontaneous MAP variations—the frequency-domain analysis and the time-domain analysis. The outcome variable COX in the time-domain analysis is a simple tool to quantify the strength of the linear relationship and is

sensitive to phase shifts between MAP and OI. The regression coefficient describes the amplification between the signals.

The frequency-domain analysis is based on the assumption that the two signals are stationary and thereby reduces the influence of noise and variance between the measurements.¹³ The coherence and gain are the outcome variables of the frequency-domain analysis and are insensitive to phase shifts. The frequency-domain analysis is less intuitive and more complicated to perform. Therefore, we intended to compare the two methods. To our knowledge, this is the first study to address the question of whether or not the two methods are equivalent.

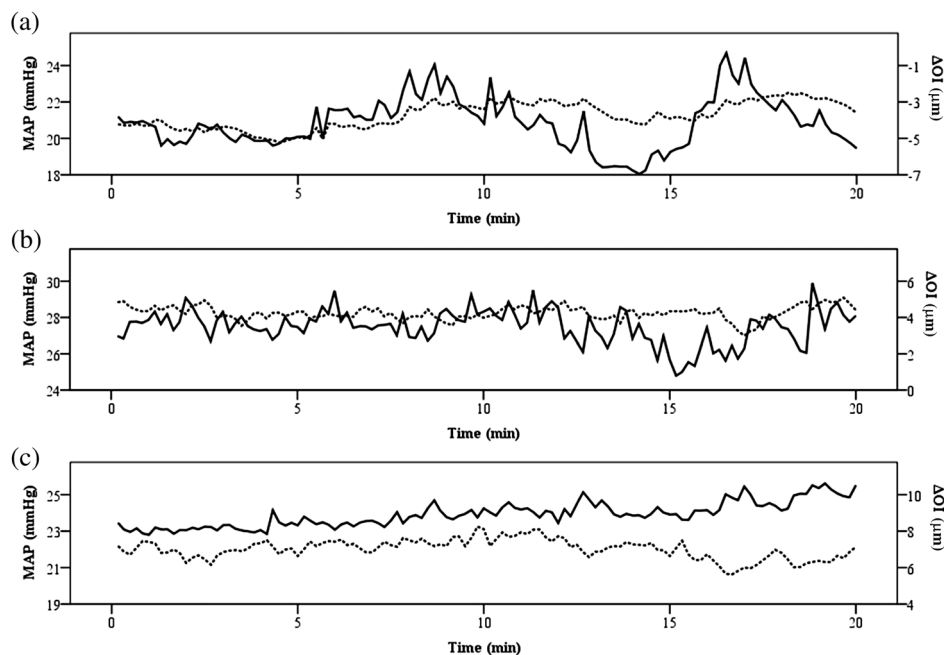


Fig. 1 Two epochs (20 min) of mean arterial blood pressure [MAP (mmHg), solid line] and oxygenation index [ΔOI (μM), dashed line]. (a) Impaired cerebral autoregulation (CA). Closely correlated MAP and OI. (b) Intact CA. OI does not follow the changes in MAP. (c) Intact CA. OI decreases while MAP increases (Note OI has a random zero).

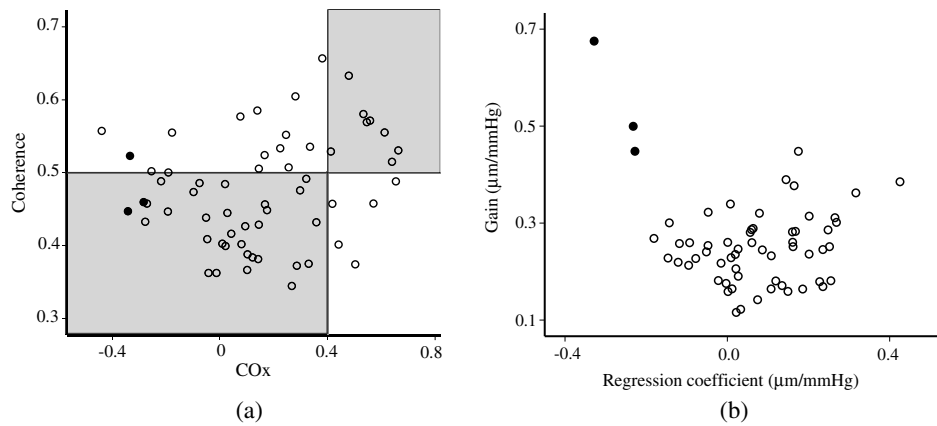


Fig. 2 The consistency between frequency-domain analysis and time-domain analysis. (a) The coherence versus cerebral oximetry index (Cox). Thresholds for impaired CA are marked by gray lines [Coherence ≥ 0.5 (Ref. 11) and COx ≥ 0.4 (Ref. 12)]. The shaded areas indicate the concordance between the two methods. (b) The gain versus regression coefficient. The three most extreme cases with high gain and negative regression coefficient are marked by solid circles.

Our data showed that the two methods did not identify the same infants with intact CA. This is also illustrated by the poor correlations between COx and coherence [Fig. 2(a)]. The correlation between the regression coefficient and gain was also weak [Fig. 2(b)] and can be explained by the fact that the correlation coefficient can assume both positive and negative values whereas gain is absolute. Hypothetically, introduced oscillations by mechanical ventilation might influence the two methods. However, when the infants were split into those who were treated with mechanical ventilation ($n = 23$) and those who were treated with nasal continuous positive pressure ($n = 37$), the poor correlation between the two methods persisted. A recently published study in adult traumatic brain injury patients concluded that the correlation between middle cerebral artery flow velocity and either cerebral perfusion pressure or MAP correlated well with Panerai's autoregulatory index and with patients' outcomes. The outcomes' variables from the frequency-domain analysis did not correlate with patient outcome.¹⁴ Other previous studies have focused on how well the different statistical methods correlate with clinical parameters and outcome.^{15–17} One study found that the absolute value of the correlation coefficient and gain was the two estimates of CA that were most robust to changes in the parameters of the analysis, i.e., the length of epochs and the percentage of overlapping subwindows.¹³

4.2 ANOVA as a Measure of Relative Repeatability

We performed an ANOVA to describe the relative repeatability because no gold standard exists when describing CA. The COx, regression coefficient, and gain had higher F -values, i.e., better relative repeatability compared with coherence (Table 1). Gain was the method with the highest F -value. The presence of multiple ways of interactions between MAP and OI with—potentially—different time delays causing different phase shifts may also explain the fact that gain of the frequency-domain analysis was the parameter with the best relative repeatability of all four parameters. When excluding the three most extreme cases with high gain and negative regression coefficients from the analysis, the F -value for gain became comparable with COx and the regression coefficient. This indicates that the signals

oscillated alike, which also leads to high repeatability in the method.

4.3 Can We Handle the Phase Shift Between the Two Signals?

Outcome variables of the time-domain analysis are sensitive to phase shifts. High gain also occurs when OI decreases as MAP increases, because gain is not able to discriminate between signals in phase or counterphase. As the coherence analysis was done in the very low frequency band, counterphase corresponds to time lags between pressure and oxygenation of 25 to 300 s. This is more than the time lag associated with normal autoregulation, which is 10 s or less.¹⁸ Therefore, sensitivity to phase shifts seems to be an advantage when the sampling frequency is low, and in this situation it may be more appropriate to consider a negative COx as an expression of intact autoregulation rather than of absent autoregulation. With autoregulation, an increase in blood pressure leads to constriction of the cerebral arteries, and hence a reduced arterio-to-venous blood volume ratio in the brain. This results in a reduction of the OI signal. Likewise, a negative regression coefficient actually quantifies that the OI is reduced as MAP increases; whereas gain might give the impression that OI increases with increasing MAP. Due to this argument, the absolute value of the correlation coefficient introduced by Caicedo et al.¹³ can be used in a mathematical sense when comparing the correlation coefficient with the coherence value—but in a physiological sense, an absolute value of the correlation coefficient does not match a physiologic concept.

The frequency-domain analysis yields a power and phase at each frequency. The phase difference, or phase shift, is a way to describe the time delay between the two signals. It has been postulated that the phase shift actually is a better way to estimate CA compared with coherence and gain in those cases where a stimulated MAP fluctuation is examined.¹⁹ Phase shift has not been reported for studies of CA in neonates based on spontaneous fluctuations in MAP.^{8,10,20–23} This might be due to the fact that the interpretation of phase over a frequency range is difficult. What does the average phase shift in a frequency band actually mean? In a group of traumatic brain injured patients, Liu et al.¹⁴ found that the phase shift correlated well with Panerai's autoregulatory index—but not with outcome.

4.4 Physiologic Interpretation of the Negative Regression Coefficient

It is normally assumed that a negative value of the regression coefficient reflects vasoconstriction of the cerebral arteries in response to increased MAP and, therefore, an intact CA. In our most extreme case [gain: $0.68 \mu\text{M}/\text{mmHg}$ and regression coefficient: $-0.33 \mu\text{M}/\text{mmHg}$, Figs. 1(c) and 2(b)], the value of the regression coefficient, however, was much higher than expected from an appropriate cerebroarterial constriction. If CA is working perfectly, arteries and arterioles constrict to increase cerebrovascular resistance in response to increased MAP. The resistance is increased in proportion to the radius to the power of 4 [resistance = $(8 * \text{viscosity} * \text{length of the vessel}) / (\pi * r^4)$]; but the volume is only reduced in proportion to the radius to the power of 2 [volume of a cylinder = $\pi * r^2 * \text{length of the vessel}$]. This vasoconstriction leads to a decrease in the arteriovenous ratio. Since OI is the difference between oxy-hemoglobin and deoxy-hemoglobin divided by a factor of 2, a decrease in the arteriovenous ratio leads to a decrease in OI. In this case, both peripheral saturation and hemoglobin were constant during the measurement. The observed increase in MAP might account for approximately one quarter of the observed decrease in OI value. Although not impossible, it is unlikely that the arteries contract much more than appropriate. Therefore, it is more likely that the reason for the MAP and OI signals being in (approximate) counterphase is that the OI was affected by other factors, i.e., the relation between the two signals was indirect, and/or not even causal. For instance, is it possible that the fluctuations in sympathetic tone drive both fluctuations in arterial blood pressure as well as in arterial and venous tones. Compared with arteries from adults, arteries from newborn infants have a denser sympathetic innervation. Furthermore, isolated middle cerebral arteries from newborn infants exhibit a stronger contraction when stimulated with norepinephrine—the transmitter of sympathetic nerve system—or sympathetic nerve stimulation.²⁴ In newborn dog puppies²⁵ and piglets,²⁶ the rise in cerebrovascular resistance in the forebrain is blocked by phentolamine or by sympathectomy. In adults, an increased diameter of the internal jugular vein has been observed when MAP increases after stimulation with phenylephrine.²⁷ This observation is most possibly caused by increased central venoconstriction and increased venous pressure, because it has been shown that the isolated cerebral veins contract in response to stimulation by noradrenaline.²⁸ Therefore, it appears plausible that the variations in sympathetic tone within 5-min time windows of the coherence and correlation analysis may result in arterial constriction and a drop in cerebral oxygenation in parallel with increased arterial pressure, as illustrated in Fig. 3. Unfortunately, sympathetic tone is difficult to monitor, but as an indirect support of this hypothesis, a strong link between cerebral oxygenation and pulse rate was recently demonstrated in infants similar to ours.²⁹

4.5 Strengths and Limitations

4.5.1 Relationship between spontaneous blood pressure variations and cerebral oxygenation

CA can be perceived as a filter that dampens the influence of MAP on CBF. To test or describe how well this filter works, fluctuations in the input signal, MAP, are needed. In adults,

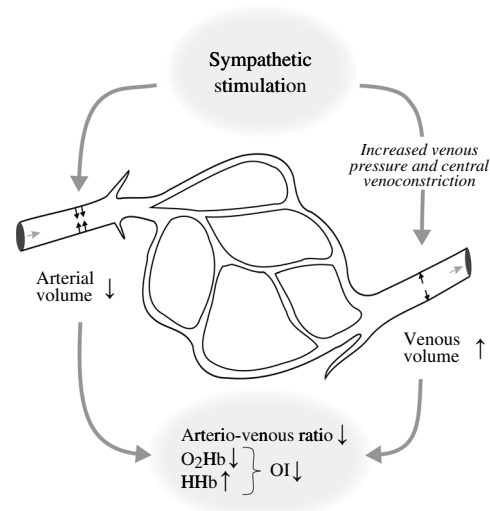


Fig. 3 A model of sympathetic tone affecting cerebral oxygenation in the immature forebrain. Increased sympathetic tone induces cerebral arterial vasoconstriction, central venoconstriction, and increased venous pressure, which lead to increased cerebral venous diameter. Hereby, the arteriovenous ratio decreases, resulting in a decrease in oxyhemoglobin (O_2Hb) and an increase in deoxyhemoglobin (HHb) concentrations. Together, this results in a decrease in oxygenation index (OI). Modified from Ref. 30.

CA can be described by stimulated MAP variations; but spontaneous MAP fluctuations are more often used in vulnerable newborn infants. The relation between MAP and OI is most likely affected by other factors. It is a principal limitation of using spontaneous blood pressure fluctuations to estimate CA that a statistically significant association between the arterial blood pressure signal and cerebral oxygenation signal does not necessarily mean that it was the changes in blood pressure that actually changed the oxygenation. There are multiple correlations among variables in the systemic and cerebral circulations including, among others heart rate, cerebral concentrations of oxy- and deoxyhemoglobin, as well as CO_2 .^{29,31} This may be true even in the clinically stable infants included in the present analysis.

Furthermore, frequency-domain analysis relies on the assumption that the signals are stationary, and this criterion is not met when spontaneous MAP fluctuations are studied. When calculating the power spectrum of the frequency domain, we used 50% overlap of the 5-min segments in each epoch. Caicedo et al.¹³ recommended 60% overlap when analyzing nonstationary signals. The present study compares two traditionally used methods of describing CA. Using 50% overlap is still the most common way of calculating the power spectrum in neonates. Furthermore, by increasing the overlap from 50% to 60%, the sensitivity index improved from 0.95 to 0.96,¹³ which was unlikely to change our results. To improve the signal-to-noise ratio, we weighted the output variables in both methods with the MAP variability within each epoch.¹¹ If the MAP variation was induced instead of spontaneous, we would expect a higher signal-to-noise ratio.

4.5.2 Cerebral oxygenation as a measure of cerebral blood flow

We used the changes in OI as a surrogate measure of changes in CBF. This is only reasonable if arterial saturation and cerebral

metabolism are stable. Infants were clinically stable during measurement, and if arterial saturation fluctuated more than 5% recordings were stopped.

COx is traditionally calculated from the correlation between MAP and cerebral tissue oxyhemoglobin saturation measured from INVOS.⁹ We used OI. Although we do not expect that this would affect the correlation between the two signals, we acknowledge that this might affect the defined threshold for impaired CA.

5 Conclusion

Our overall conclusion is that high gain and high coherence may arise spuriously when cerebral oxygenation decreases as blood pressure increases at low frequency by mechanisms unlikely to be related to autoregulation. Hence, time-domain analysis appears a more robust—and simpler—method to describe CA.

Acknowledgments

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Gorm Greisen is a consultant neonatologist and a professor of pediatrics. His research has focused on cerebral blood flow and oxygenation in preterm infants during since 1982.

Biographies of the other authors are not available.