Cerebral Tissue Oxygenation and Regional Oxygen Saturation Can Be Used to Study Cerebral Autoregulation in Prematurely Born Infants

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ABSTRACT: The coupling of cerebral intravascular oxygenation (dHbD) with mean arterial blood pressure (MABP) was taken as a reflection of autoregulation assuming constant arterial oxygen content. However, this method is sensitive to movement artifacts. We examined whether the cerebral tissue oxygenation index (cTOI) and regional oxygen saturation (rScO₂) may replace dHbD and changes in total Hb (dHbT), respectively. Correlation (COR) and coherence (COH) were used to measure the agreement of MABP with rScO₂/dHbT and cTOI/dHbD. dHbD/cTOI and dHbT/rScO₂ recordings of, respectively, 34 and 20 preterm infants in need for intensive care were studied during the first days of life. dHbD and cTOI were obtained with the NIRO300 and rScO₂ and dHbT with the INVOS4100. Invasive MABP was measured continuously. COR and COH scores of MABP *versus* dHbD/dHbT were compared with the corresponding ones by replacing dHbD/dHbT by cTOI/rScO₂, respectively. Generally, no significant score differences were found for dHbD/cTOI. Differences for dHbT/rScO₂ were slightly larger but still within the normal variation of the parameters. Differences become insignificant when restricting calculations to epochs of larger variation in MABP (>10 mm Hg). Hence, we suggest that cTOI and rScO₂ can be used to study cerebral autoregulation in newborns. (*Pediatr Res* 69: 548–553, 2011)

Lassen (1) was the first to describe cerebral autoregulation in man. Cerebral autoregulation is a property of arteries in the brain to constrict in response to an increase in transmural blood pressure and to dilate in response to a decrease in blood pressure, with the effect of keeping blood flow more or less constant within a range of arterial blood pressures. This response has a limited capacity and as a result blood flow will decrease or increase when blood pressure decreases below a lower threshold or increases above an upper threshold, respectively (2). Pryds *et al.* (3) described a loss of autoregulation in very sick preterm infants, which resulted in the hypothesis that there was a loss of autoregulation in preterm infants and that controlling blood pressure would prevent cerebral damage. However, there is no good evidence that a correlation (COR) between blood pressure and

cerebral damage exists, indicating that autoregulation is more complex in premature infants than originally thought (4). Even with very low blood pressures, normal cerebral blood flow (CBF) was described in very LBW infants (5). Both dynamic and static autoregulation are described. Dynamic autoregulation describes the response of autoregulation within 5 to 10 s after a change in blood pressure and can be assessed noninvasively with Doppler ultrasound (6–8) and near-infrared spectroscopy (NIRS) (9). Tsuji *et al.* (10) were the first to report on the use of NIRS to assess autoregulation. In a previous study (11), the authors validated changes in the cerebral intravascular oxygenation (dHbD) as a measure of CBF in an experimental model. dHbD, representing the difference between changes in oxygenated (dHbO₂) and reduced (dHbR) Hb, can be continuously measured by means of any NIRS device providing the raw optical densities and slope data. Tsuji *et al.* (10) found a high COR between dHbD and mean arterial blood pressure (MABP) changes, indicating loss in autoregulation. A high COR was found between intact autoregulation and outcome, *i.e.* the frequency of severe intraventricular bleedings. Moreover, Wong *et al.* (12) found that high coherence (COH) between MAP and TOI indicates impaired cerebral autoregulation in clinically sick preterm infants and is strongly associated with subsequent mortality. However, dHbD is a relative parameter and difficult to measure because of movement artifacts. If we want to have a continuous robust measurement, other parameters of oxygenation should be used. The cerebral tissue oxygenation index (cTOI) and the cerebral regional oxygen saturation (rScO₂) are two promising NIRS parameters that provide absolute values of regional Hb oxygen saturation in absolute terms. In addition, they are less prone to movement artifacts (13). cTOI is based on spatially resolved spectroscopy and calculated by $(\text{kHbO}_2/\text{kHbT}) \times 100 (\%)$, where HbO₂, HbR, and HbT denote, up to an unknown scaling factor k, the absolute

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Abbreviations: CBF, cerebral blood flow; COH, coherence; COR, correlation; cTOI, cerebral tissue oxygenation index; dHbD, cerebral intravascular oxygenation; dHbO₂, changes in oxygenated Hb; dHbR, changes in reduced Hb; dHbT, changes in total Hb; HbO₂, oxygenated Hb; HbT, total Hb; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; PMA, postmenstrual age; rScO₂, cerebral regional oxygen saturation; SaO₂, arterial oxygen saturation

concentration of, respectively, oxygenated Hb, reduced Hb, and total Hb ($\text{HbT} = \text{HbO}_2 + \text{HbR}$) (14). rScO_2 is calculated by a proprietary algorithm, which is also based on spatially resolved spectroscopy (15). Both cTOI and rScO_2 are absolute values and have been validated against the jugular venous saturation and each other (16,17). In this study, we examined whether cTOI and rScO_2 can replace dHbD and dHbT , respectively, in the measurement of autoregulation.

METHODS

A total of 54 infants with need for intensive care were monitored during the first days of life at the NICU of two different hospitals. Their recordings were collected in three different datasets. In the first dataset, a total of 14 infants from the NICU of the University Hospital Leuven, Belgium, were included. These infants with a mean postmenstrual age (PMA) of 37 6/7 wk (27–47) and a mean body weight of 2931 g (855–4380) were treated with propofol to attain a short-lasting sedation during elective chest tube removal to facilitate chest tube removal and avoid external aspiration of air. This dataset, called the propofol dataset in this article, was also used in a separate study presented in Ref. 18. The second dataset contains the recordings of 20 prematurely born infants with need for intensive care that were monitored during the first 3 d of life at the same NICU of the University Hospital Leuven, and it will be referred to as the Leuven dataset. Mean PMA of the Leuven infants was 28 5/7 wk ($\text{SD} \pm 3$ 2/7), mean body weight was 1125 g ($\text{SD} \pm 503.76$), and mean postnatal age (PNA) at the time of measurements was 1.4 d ($\text{SD} \pm 1.06$). Cranial ultrasounds are performed at d 1, 3, and 7 or more frequently if needed.

The third dataset includes the recordings of 20 prematurely born infants monitored at the NICU of the University Medical Centre Utrecht, The Netherlands. These infants had a mean PMA of 29 2/7 wk ($\text{SD} \pm 1$ 2/7), mean PNA at the time of measurements 2 d ($\text{SD} \pm 1$), and a mean body weight of 1114 g ($\text{SD} \pm 316.94$). This dataset will be referred to as the Utrecht dataset. Demographic and clinical data for all infants are summarized in Table 1. Cranial ultrasounds are performed at d 1, 2, 3, and then weekly.

The medical ethical committee of the University Hospital Gasthuisberg in Leuven and the Wilhelmina Children's Hospital in Utrecht approved this study. Informed parental consent was obtained in all cases.

Vital signs. Arterial oxygen saturation (SaO_2) was continuously recorded by pulse oxymetry on a limb and MABP by an indwelling arterial catheter (umbilical, tibial, or radial artery).

Cerebral hemodynamics. In Leuven, the NIRO300 device (Hamamatsu, Japan) was used for the noninvasive monitoring of cerebral hemodynamic and oxygenation parameters cTOI , dHbO_2 , and dHbR . The differential path length factor (taking into account the scattering of the near-infrared light into the brain) was set at 4.39 (19,20) and encoded into the computer as a constant value. For calculation of cTOI , the absorption of near-infrared light is measured at three points, and the diffusion equation is used. dHbD was calculated afterward as the difference between dHbO_2 and dHbR .

In Utrecht, with the INVOS4100 instrument (Somanetics Corp, Troy, MI), rScO_2 and the optical densities at a distance 4 cm (deep signal) and 3 cm (shallow signal) from the detector were recorded simultaneously. For the calculation of rScO_2 , the scattering of near-infrared light at two wavelengths, namely 730 and 810 nm, is measured at 3 cm and deducted from the measurement at the second optode at 4 cm. dHbT was computed afterward as the inverse of the difference between deep and shallow OD signals at 810 nm (21).

Signal processing. MABP and SaO_2 data in Leuven were generated at 2 Hz and recorded at a sampling frequency of 100 Hz by a data acquisition system CODAS (Dataq Instruments) and stored on a computer. The NIRO 300 signals are digital and recorded with a sampling frequency of 6 Hz. They were converted to analog signals with a sample-and-hold function before being introduced in the CODAS system (Dataq Instruments). To ensure the best comparability between both medical centers, we downsampled these signals to the same frequency of 0.0167 Hz (periodicity 60 s). This low frequency was dictated by the sampling frequency of the dHbT signal (one sample per minute). Moreover, to reduce the loss of information in the new downsampled signal, the signals were first filtered with a mean average filter. In addition, to study the influence of the sampling frequency on the scores, we also analyzed the NIRO data after filtering and downsampling to 0.333 Hz (periodicity 3 s).

In Utrecht, MABP, SaO_2 , and rScO_2 were collected simultaneously by the Poly5 system (Inspektor Research Systems, The Netherlands) with a sampling frequency of 10 Hz and stored on a personal computer for offline analysis. The rScO_2 was recorded using the INVOS4100 with a sampling frequency of 0.25 Hz. The signal was then converted to an analog signal with a sample-and-hold function before being introduced in the Poly5 system. Because the optical densities were sampled at 0.0167 Hz (*i.e.* one value per minute) on a separate disk drive, all signals were filtered with a mean average filter and then downsampled to this lower frequency to avoid loss of information in the new downsampled signal. By adopting this new sample frequency, we stay in accordance with the findings of von Siebenthal *et al.* (22) concerning the periodicity of the studied signals. A similar study of the influence of the sampling frequency on the scores, as with the NIRO300 data, was not possible with the INVOS4100 data because of the low sample frequency of dHbT .

To all data from both centers, a preprocessing algorithm was applied to remove measurement artifacts induced by medical interferences as follows. First, as described by Soul *et al.* (23), each artifact point from the hemodynamic data was removed. To remove occasional artifacts such as movements and displacements in the baseline, we developed a novel robust function estimator described in Ref. 24. This algorithm, programmed in Matlab (Mathworks, Natick, MA), trained a Least Squares Support Vector Machine (LS-SVM) to interpolated data as long as the duration of the artifact was shorter than 30 s (25), otherwise the signal was truncated. Hence, a continuous recording was divided in smaller segments free of artifacts. Only segments with length longer than 40 min were kept for further analysis. In addition, we divided the signal in nonoverlapping 20-min epochs. Next, we kept the signals in normal physiological ranges, particularly SaO_2 in the range 87–95% (in this way the condition of constant SaO_2 is nearly satisfied). Finally, we deleted remaining artifact spikes, which could not be detected in the previous step. Figure 1 displays typical recordings of SaO_2 , MABP, dHbD , and cTOI as measured on a preterm infant in Leuven.

COH and COR. COR has been absolute valued such that its value matches the interval [0,1] (0–100%) instead of [−1,1] for comparability with the COH method. We computed COH using the Welch's averaged periodogram method (26). The COR and the average of COH over the frequency band 0.0042–0.00837 Hz (periodicity in the range 240–120 s) for the 60 s data, and over the frequency band 0.0033–0.04 Hz for the 3 s data (range 300–25 s, because of the use of an antialiasing low-pass filter with cutoff frequency of 0.04 Hz) (23), were used as scores for the considered signal epoch (22,27–29). Because the COR and COH values between the signals might vary as a function of time, a sliding window approach was used. Both scores were calculated over 20-min epochs. To calculate the amplitude of the COH, the autopower and crosspower spectra densities were estimated using the Welch's averaged periodogram method. In this method, each 20-min epoch was subdivided into five segments of duration 10 min with an overlap of 7.5 min.

Table 1. Characteristics for the Leuven, Utrecht, and Propofol dataset

Clinical characteristic	Leuven dataset	Utrecht dataset	Propofol dataset
Body weight (g)	1007 (570–2935)	1025 (640–1690)	2931 (855–4380)
GA (wk)	29 2/7 (24–39)	29 3/7 (26–31)	35 3/7 (26–40)
Male/female	10/10	10/10	16/4
Apgar 1	7 (0–9)	6 (1–9)	7 (4–9)
Apgar 5	9 (1–10)	8.5 (4–10)	8 (4–10)
IVH, <i>n</i> (%)	7 (35)	4 (20)	0 (0)
PVL, <i>n</i> (%)	7 (35)	1 (5)	0 (0)
Neonatal mortality, <i>n</i> (%)	1 (5)	1 (5)	0 (0)
Number of 20-min epochs	4 (1–15)	12 (4–36)	1 (1–2)

Median (range) unless otherwise stated.

IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

Figure 1. Typical recordings of SaO_2 , MABP, dHbD, and cTOI as measured on a preterm infant in Leuven.

Figure 2. Bland-Altman plot for COH scores (dHbD/MABP and cTOI/MABP), averaged per child, in the Leuven dataset sampled at 60 s. The central line corresponds to the mean difference and the lower and upper line to ± 1.96 the SD.

Statistical analyses. The scores computed from cTOI versus MABP (method 1) and dHbD versus MABP (method 2) can be considered as two measurements from the same underlying process. Similarly, the scores computed from rScO₂ versus MABP (method 1) and dHbT versus MABP (method 2), using the recordings from Utrecht, can be considered as two measurements of the same process. Two different analyses were performed on patient level (with one mean value per patient) and epoch level (with one score value for each 20-min epoch). On the patient level, the scores were averaged for babies of whom multiple 20-min epochs were available, to obtain one mean score value per baby. The paired *t* test and Wilcoxon signed-rank test were applied to investigate the difference in the mean COR and mean COH score between 1) cTOI/MABP and HbD/MABP and 2) rScO₂/MABP and dHbT/MABP. On the epoch level, generalized linear mixed models were used to take into account the scores over all 20-min epochs (multiple measurements) per baby. In addition, to study the influence of the variations in MABP in cerebral autoregulation assessment, the scores corresponding to epochs with high variations in MABP were analyzed separately (MABP >10 mm Hg). Bland-Altman plots were constructed to visualize the agreement between the two methods, as shown in Figs. 2–4. All reported *p*-values were two-tailed and we considered as statistically significant a nominal *p*-value <0.05. The statistical analyses were performed using the SAS system (version 9.1; SAS Institute Inc., Cary, NC).

RESULTS

Mean recording time for the propofol, Leuven, and Utrecht dataset was, respectively, 1 h and 32 min (SD $\pm$ 42 min), 1 h

Figure 3. Bland-Altman plot for COH scores (dHbD/MABP and cTOI/MABP), averaged per child, in the propofol dataset sampled at 60 s. The central line corresponds to the mean difference and the lower and upper line to ± 1.96 the SD.

Figure 4. Bland-Altman plot for COH scores (dHbT/MABP and rScO₂/MABP), averaged per child, in the Utrecht dataset sampled at 60 s. The central line corresponds to the mean difference and the lower and upper line to ± 1.96 the SD.

and 48 min (SD $\pm$ 70 min), and 05 h and 25 min (SD $\pm$ 3 h and 13 min).

Analysis including mean COR and mean COH scores per patient. In Table 2, the differences in mean scores computed from dHbD (respectively, dHbT) versus MABP (method 1) compared with cTOI (respectively, rScO₂) versus MABP (method 2) were assessed. All data were sampled at 60 s. For the propofol dataset, mean COR and mean COH, computed from dHbD versus MABP compared with cTOI versus MABP, were not statistically different ($p = 0.22$ and $p = 0.45$, respectively). For the Leuven dataset, the corresponding mean COR scores were not statistically different ($p = 0.40$), whereas the corresponding mean COH scores were statistically different ($p = 0.04$) with a difference of 5.5%. However, these differences remain clinically unimportant and fall within the normal variation of the parameters. This implies that both methods can be used interchangeably.

For the Utrecht dataset, mean COR and mean COH scores, computed from dHbT versus MABP compared with rScO₂

Table 2. COR and COH scores computed from dHbD (respectively, dHbT) vs MABP (method 1) compared with cTOI (respectively, rScO₂) vs MABP (method 2)

	<i>p</i>	Method 1		Method 2	
		Mean ± SD	Median (minimum-maximum)	Mean ± SD	Median (minimum-maximum)
Propofol					
COR score	0.22	45.6 ± 21.0	43.1 (14.9–82.2)	39.1 ± 17.2	35.7 (12.6–69.4)
COH score	0.45	47.2 ± 17.4	45.8 (16.0–80.9)	44.2 ± 12.1	46.3 (21.1–57.3)
Leuven					
COR score	0.40	42.2 ± 10.2	40.1 (29.1–67.1)	39.7 ± 10.4	38.2 (19.3–59.9)
COH score	0.04	44.2 ± 11.3	42.1 (23.7–64.5)	38.7 ± 8.5	39.8 (18.9–58.6)
Utrecht					
COR score	<0.01	32.4 ± 5.0	33.8 (22.6–42.4)	41.7 ± 7.6	40.0 (31.5–65.6)
COH score	0.01	33.0 ± 7.9	31.3 (18.0–48.0)	38.8 ± 7.0	36.6 (27.8–55.0)

All data were sampled at 60 sec and scores given in percentage.

Table 3. COR and COH scores computed from dHbD (respectively, dHbT) vs MABP (method 1) compared with cTOI (respectively, rScO₂) vs MABP (method 2) for all epochs per patient

	<i>p</i>	Method 1		Method 2	
		Mean ± SD	Median (minimum-maximum)	Mean ± SD	Median (minimum-maximum)
Propofol 60 s data (<i>n</i> = 53, 14 babies)					
COR score	0.21	46.5 ± 29.8	44.6 (0.1–99.8)	39.8 ± 27.6	34.2 (0.8–88.3)
COH score	0.38	48.0 ± 22.4	47.9 (8.3–95.4)	44.7 ± 20.2	43.5 (4.1–91.0)
Leuven 60 s data (<i>n</i> = 284, 20 babies)					
COR score	0.95	43.1 ± 24.1	40.5 (0.8–94.7)	43.2 ± 23.2	43.3 (0.2–94.7)
COH score	0.08	42.8 ± 24.5	39.9 (2.2–96.8)	39.3 ± 22.1	38.2 (0.9–93.9)
Utrecht 60 seconds data (<i>n</i> = 342, 20 babies)					
COR score	<0.01	31.9 ± 21.0	28.6 (0.1–82.3)	41.6 ± 25.0	41.9 (0.04–95.8)
COH score	<0.01	31.3 ± 19.3	29.8 (0.5–87.1)	38.8 ± 23.3	35.9 (0.6–97.8)

The scores are given in percentage. The number of considered 20-min epochs is denoted by *n*.

Table 4. COR and COH scores computed from dHbD (respectively, dHbT) vs MABP (method 1) compared with cTOI (respectively, rScO₂) vs MABP (method 2) for 20-min epochs with variations in MABP > 10 mm Hg

	<i>p</i>	Method 1		Method 2	
		Mean ± SD	Median (minimum-maximum)	Mean ± SD	Median (minimum-maximum)
Propofol 60 s data (<i>n</i> = 14, 8 babies)					
COR score	0.96	55.2 ± 28.4	55.0 (12.7–99.8)	54.7 ± 26.3	69.5 (9.3–83.4)
COH score	0.76	44.0 ± 23.9	42.3 (8.3–95.4)	41.7 ± 23.5	39.4 (13.0–91.0)
Leuven 60 seconds data (<i>n</i> = 46, 15 babies)					
COR score	0.57	47.1 ± 26.7	50.2 (1.3–92.7)	44.2 ± 25.5	46.8 (3.7–93.1)
COH score	0.68	46.1 ± 27.8	45.0 (4.0–96.8)	43.8 ± 25.3	44.0 (3.3–91.3)
Utrecht 60 s data (<i>n</i> = 62, 15 babies)					
COR score	0.09	35.4 ± 22.9	35.2 (0.1–74.7)	43.1 ± 27.0	42.0 (0.04–92.5)
COH score	0.21	35.3 ± 20.7	33.8 (0.8–82.6)	40.3 ± 25.9	37.7 (1.1–97.8)

Scores are given in percentage. The number of considered 20-min epochs is denoted by *n*.

versus MABP, were statistically different ($p \leq 0.01$), with differences 9.3 and 5.8%, respectively. Bland-Altman plots of the COH scores for the Leuven, propofol, and Utrecht datasets are shown in Figs. 2, 3, and 4, respectively.

Analysis including all the scores over all epochs. Table 3 shows the *p*-values pointing out the statistical significance of the differences in scores computed from dHbD (respectively, dHbT) versus MABP (method 1) compared with cTOI (respectively, rScO₂) versus MABP (method 2). Here, the scores are compared for each 20-min epoch. For each baby, multiple measurements are available. Generalized linear mixed models were used to assess the differences between both methods.

In the propofol dataset, the differences in COR and COH scores, computed from dHbD versus MABP compared with cTOI versus MABP, were not statistically significant ($p = 0.21$ and $p = 0.38$). Similar insignificant differences hold for the Leuven dataset ($p = 0.95$ and $p = 0.08$).

For the Utrecht dataset, the differences in COR and COH scores, computed from dHbT versus MABP compared with rScO₂ versus MABP, were statistically significant ($p < 0.01$ in both cases), with differences 9.7 and 7.5%, respectively.

Analysis including the scores over 20-min epochs with high variations in MABP. Table 4 shows a similar analysis as in Table 3, except that only 20-min epochs with a high

variation in MABP (>10 mm Hg) were retained for the calculations.

In the propofol dataset, the COR and COH scores, computed from dHbD *versus* MABP compared with cTOI *versus* MABP, were not statistically different ($p = 0.96$ and $p = 0.76$, respectively). Similar results hold for the Leuven dataset (with $p = 0.57$ and $p = 0.68$, respectively). Moreover, for the Utrecht dataset, the differences in COR and COH scores, computed from dHbT *versus* MABP compared with rScO₂ *versus* MABP, were no longer statistically significant (with $p = 0.09$ and $p = 0.21$, respectively).

For completeness of the study, we also used dHbT instead of dHbD in the whole analysis and comparison of both methods using the two cohorts of Leuven. No significant differences for the propofol dataset between dHbD/MABP and dHbT/MABP were found. For the Leuven dataset, differences in mean COH score are significant ($p < 0.008$) and below 5%, whereas differences in mean COR scores were larger (up to 17%). These results are not included for conciseness of the article.

Analysis including mean scores per patient and all epochs per patient using data sampled at 3 s. To study the influence of the sampling frequency on the scores, the differences in mean scores (COR and COH), computed from dHbD *versus* MABP (method 1) compared with cTOI *versus* MABP (method 2), in the propofol and the Leuven datasets were analyzed on a patient level, and on epoch level. Although p -values were lower, similar conclusions hold as for the 60-s data. Wherever differences were statistically significant, they always remained lower than 5.6%.

DISCUSSION

Impaired cerebral autoregulation is considered a risk factor for brain injury in the sick premature infant (2,10,12,23). However, previous studies using intermittent static measurements (5) showed that CBF is independent from MABP over a wide pressure range in premature babies. When there is a lack of autoregulation, oxygen delivery is a function of CBF and cerebral arterial oxygen content. Hence, it would be of clinical interest to have a continuous measure of autoregulation. Therefore, NIRS was used by Tsuji *et al.* (10). Tsuji *et al.* (11) and Soul *et al.* (30) validated HbD as a good measure of CBF. Moreover, as total Hb (HbT) reflects changes in cerebral blood volume (CBV) (31) in patients with lack of autoregulative properties, as the ones included in this study, it is possible that HbT reflects CBF. The main problem of these measurements is that they are very sensitive to movements and thus only applicable in research settings. More recently, spatially resolved spectroscopy introduced new parameters like cTOI and rScO₂, reflecting Hb oxygen saturation predominantly of the venous compartment (32). These parameters are less sensitive to movements and provide absolute values.

As shown in Tables 2–4, no important differences exist in using cTOI instead of dHbD and using rScO₂ instead of dHbT for the measurement of autoregulation. The NIRS-derived parameter dHbT has been validated as a measure of blood volume, so it does not represent changes in blood flow.

Because data were obtained in stable infants, changes in CBF and CBV could be expected to be equivalent, as confirmed in our study. Significant differences, if any, in mean COR and mean COH scores between both methods are less than 7% when sampling the data at 60 s, which is still within the normal variation induced for the NIRS parameters (13). Using rScO₂ instead of dHbT as measure for autoregulation, larger differences (up to 9.7%) were noticed. This can be produced for the difficulties in measuring dHbT using the INVOS4100 (this value is not user-accessible and was highly sensitive to artifacts) or because dHbT less reflects CBF compared with dHbD (11); however, there is no evidence to prove these assumptions. These differences can still be considered as normal, therefore, clinically unimportant when used, *e.g.* for detection of impaired autoregulation. However, all these differences become insignificant when only the larger variations in MABP (>10 mm Hg) are taken into account for the calculation of the COH and COR scores, as presented in Table 4. Small changes in MABP yield low values in their power spectral density. Because our COH/COR score calculations are using spontaneous MABP changes, a lot of which are small, these might affect their reliability as confirmed by Hahn *et al.* (33). Therefore, these epochs of higher MABP variations enable a more reliable detection of (im)paired autoregulation. They better assess the autoregulative properties of the brain and are clinically more important.

Even though there are no important statistical differences between the methods, large discrepancies in the COR and COH values on an infant-to-infant basis exist, as depicted in the Bland-Altman plots (Figs. 2–4). Hence, the agreement is not very high either. These discrepancies, as mentioned before, can be attributed to the normal variations of the NIRS parameters and to the fact that model assumptions are only approximately valid in practice. The NIRS parameters only indirectly measure CBF and their coupling with MABP approximately reflects autoregulation assuming SaO₂ constant, which is only approximately valid. More importantly, what really matters here is the lower sensitivity of cTOI and rScO₂ to movement artifacts compared with dHbD and HbT. Therefore, they represent a more robust variable to assess the autoregulation status of the infants.

Hence, this enables the direct clinical use of signal processing methods for the automated and continuous calculation of the coupling between dHbD/cTOI and dHbT/rScO₂ *versus* MABP, using NIRS, mostly by means of COR and COH. However, these scores are not a precise measurement of autoregulation but rather a reflection of the autoregulation status of the baby.

It is important to recognize here the potential limitations of the use of COR and the COH analysis to investigate moment-to-moment autoregulation mechanisms, because these approaches assume a linear and stationary relationship between the measured NIRS signals and MABP, which can produce misleading results in a system with nonlinear and nonstationary properties. Future research should be oriented to evaluate these effects.

Finally, the scores should be related to clinical outcome of the infants. The scores of our propofol dataset are shown to be

related to clinical intervention because they change concordant to the administration of propofol (18). No other conclusions can be drawn because the populations used here are too small. However, this is part of ongoing research, and the results will be published elsewhere.

CONCLUSIONS

Little or no statistical differences are found between mean COR and mean COH scores computed from dHbD *versus* MABP compared with cTOI *versus* MABP using NIRO300 recordings from Leuven and between scores computed from dHbT *versus* MABP compared with rScO₂ *versus* MABP using INVOS4100 recordings from Utrecht, although large discrepancies exist on an infant-to-infant basis. Using three different datasets, recorded in two different centers Leuven and Utrecht with two different devices and sampled at two different rates 3 and 60 s, we showed a similarity in scores by replacing the measured NIRS signal dHbD by cTOI when using a NIRO300 instrument and by replacing dHbT by rScO₂ when using an INVOS4100 instrument. Hence, cTOI and rScO₂ can be used for the calculation of cerebral autoregulation in neonates. Moreover, as the frequency range is restricted to lower frequencies (smaller than 0.008 Hz), we showed that the correspondences between the scores derived from dHbD and cTOI or dHbT and rScO₂, increase. These correspondences further increase when restricting the COH/COR score calculations to those epochs with large enough variations in MABP (>10 mm Hg).

The next step will be to generate software to use these parameters online in patients and to study the autoregulation in different situations in clinical practice. The importance of these findings is that we now have a reliable monitor to measure cerebral autoregulation noninvasively and continuously in preterm infants. Whether this parameter can help us in treating patients and prevent cerebral complications will have to be studied in the future.

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