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Wolfsberger, Christina Helene ; Avian, Alexander ; Schwaberger, Bernhard ; Pichler, Gerhard ; Wolf, Martin ; Urlesberger, Berndt

Abstract: AIM To investigate cerebral blood volume (CBV) in preterm neonates using time-resolved near-infrared spectroscopy. METHODS In this prospective observational study, time-resolved near-infrared spectroscopy measurements of CBV using tNIRS-1 were performed in 70 preterm neonates. For measurements, a sensor was placed for a duration of 1 min, followed by four further reapplications of the sensor, overall five measurements. RESULTS In this study, 70 preterm neonates with a mean ± SD gestational age of 33.4 ± 1.7 weeks and a birthweight of 1931 ± 398 g were included with a postnatal age of 4.7 ± 2.0 days. Altogether, 2383 CBV values were obtained with an overall mean of 1.85 ± 0.30 mL/100 g brain. A total of 95% of the measured CBV values varied in a range from -0.31 to 0.33 from the overall individual mean. Taking the deviation of the mean of each single application for each patient, this range reduced from -0.07 to 0.07. The precision of the measurement defined as within-variation in CBV was 0.24 mL/100 g brain. CONCLUSION The overall mean CBV in stable preterm neonates was 1.85 ± 0.30 mL/100 g brain. The within-variation in CBV was 0.24 mL/100 g brain. Based on the precision obtained by our data, CBV of 1.85 ± 0.30 mL/100 g brain may be assumed as normal value for this cohort.

DOI: https://doi.org/10.1111/apa.17040

Received: 21 August 2023 | Revised: 5 November 2023 | Accepted: 7 November 2023

DOI: 10.1111/apa.17040

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Precision and normal values of cerebral blood volume in preterm neonates using time-resolved near-infrared spectroscopy

Christina Helene Wolfsberger[1,2,3] | Alexander Avian[4] | Bernhard Schwaberger[1,2,3] | Gerhard Pichler[1,2,3] | Martin Wolf[5] | Berndt Urlesberger[1,2,3]

[1]Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

[2]Research Unit for Neonatal Macro- and Microcirculation, Medical University of Graz, Graz, Austria

[3]Research Unit for Cerebral Development and Oximetry Research, Medical University of Graz, Graz, Austria

[4]Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

[5]Biomedical Optics Research Laboratory, Department of Neonatology, University of Zurich, University Hospital Zurich, Zurich, Switzerland

Correspondence
Christina Helene Wolfsberger, Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Auenbruggerplatz 34/2, Graz 8036, Austria.
Email: christina.wolfsberger@medunigraz.at

Abstract

Aim: To investigate cerebral blood volume (CBV) in preterm neonates using time-resolved near-infrared spectroscopy.

Methods: In this prospective observational study, time-resolved near-infrared spectroscopy measurements of CBV using tNIRS-1 were performed in 70 preterm neonates. For measurements, a sensor was placed for a duration of 1 min, followed by four further reapplications of the sensor, overall five measurements.

Results: In this study, 70 preterm neonates with a mean ± SD gestational age of 33.4 ± 1.7 weeks and a birthweight of 1931 ± 398 g were included with a postnatal age of 4.7 ± 2.0 days. Altogether, 2383 CBV values were obtained with an overall mean of 1.85 ± 0.30 mL/100 g brain. A total of 95% of the measured CBV values varied in a range from −0.31 to 0.33 from the overall individual mean. Taking the deviation of the mean of each single application for each patient, this range reduced from −0.07 to 0.07. The precision of the measurement defined as within-variation in CBV was 0.24 mL/100 g brain.

Conclusion: The overall mean CBV in stable preterm neonates was 1.85 ± 0.30 mL/100 g brain. The within-variation in CBV was 0.24 mL/100 g brain. Based on the precision obtained by our data, CBV of 1.85 ± 0.30 mL/100 g brain may be assumed as normal value for this cohort.

KEYWORDS
cerebral blood volume, normal value, precision, preterm neonates, time-resolved NIRS

1 | INTRODUCTION

Cerebral blood volume (CBV) has gained increasingly interest as an additional parameter that provides information about cerebral haemodynamics in neonates.[1] Within the first minutes after birth, a decrease of CBV has been observed, which might be a result of changes in partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2). Changes in pO_2 and pCO_2 have an impact on

Abbreviations: CBV, cerebral blood volume; Hb, haemoglobin; Hb_{tot}, total haemoglobin; NIRS, near-infrared spectroscopy; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

cerebral vessel diameter, as lower pO_2 values stimulates vasodilation, which further influences CBV and cerebral blood flow.[1,2] Thus, changes in CBV can be a result of alterations of cerebral perfusion, which further might be associated with brain injury, especially in vulnerable preterm neonates.[3,4]

Various invasive and non-invasive methods for evaluation of cerebral haemodynamics including CBV are available. These include positron emission tomography, magnetic resonance imaging, Doppler sonography or near-infrared spectroscopy (NIRS). NIRS enables a continuous and non-invasive measurement of oxygenated and deoxygenated haemoglobin.[5] Using the spatially resolved NIRS technique only relative changes of CBV (ΔCBV) can be calculated, whereas the time-resolved NIRS technique allows the measurement of absolute total haemoglobin (Hb_{tot}) values, and consecutively, the calculation of an absolute CBV value. In several studies[1,3,6] ΔCBV was measured by NIRS using spatially resolved technique; however, only a few publications exist using time-resolved NIRS technique.[7,8] ΔCBV can be calculated, in proportion to Hb_{tot} concentrations, under the assumption of a constant haemoglobin (Hb) and cerebral-to-large vessel haematocrit ratio.[1]

Studies have already described the importance of reproducibility of measurements of cerebral haemodynamics using NIRS. Avian et al.[9] investigated the precision of cerebral oxygen saturation (time-resolved NIRS) in stable preterm neonates performed by five reapplications. They observed that time-resolved NIRS measurements for cerebral oxygen saturation were precise with a within-patient variation below the threshold of 5%. Kleiser et al.[10] described that the precision of cerebral oxygen saturation measurements, using spatially resolved NIRS, were improved by the exclusion of patients with motion artefacts. This is further, in accordance with Pichler et al.,[11] who described the within-patient variance before and after removal of implausible values, also using spatially resolved NIRS.

Due to the importance of precision of measurements of cerebral haemodynamic parameters, several studies described reproducibility of various NIRS oximeters, focusing on cerebral oxygen saturation.[9–13] For CBV there are huge ranges of estimated normal values. Furthermore, data on precision of CBV measured with time-resolved NIRS in stable preterm neonates are lacking.

Therefore, the aim of the present study was to evaluate CBV in stable preterm neonates and to investigate the precision of CBV using time-resolved NIRS.

Key Notes

- There are huge ranges of estimated normal values for cerebral blood volume in neonates.
- Data on precision of cerebral blood volume measured with time-resolved near-infrared spectroscopy in stable preterm neonates are lacking.
- Based on the precision obtained by data in this study, our described cerebral blood volume of 1.85 ± 0.30 mL/100 g brain may be assumed as normal value for stable preterm neonates at the neonatal intensive care unit.

2 | METHODS

2.1 | Study design

This observational study analysed the data which were collected during a prospective observational study that was conducted at the neonatal intensive care unit of the Division of Neonatology, Medical University of Graz. The study was approved by the Regional Committee on Biomedical Research Ethics (EC-Number: 29–351 ex 16/17) and written informed consent was obtained from the parents before inclusion into the study. The measurements were performed by a trained study team at the neonatal intensive care unit on stable preterm neonates with a gestational age of less than 37 weeks within the first week after birth. We excluded neonates with need for any respiratory support, supplemental oxygen, compromised cardio-circulatory condition requiring inotropes or vasopressors, severe cerebral injuries, defined as intraventricular haemorrhage greater than grade II, stroke, hypoxic–ischemic encephalopathy > grade I and major congenital malformations. Further, preterm neonates with abnormal haemoglobin values, which were postnatally obtained from routine blood samples, were excluded.

2.2 | Near-infrared spectroscopy

Time-resolved NIRS measurements were performed using the portable tNIRS-1 (Hamamatsu Photonics K.K., Hamamatsu, Japan). tNIRS-1 uses a time-correlated single-photon counting technique for detection.[7] For measurements, three different wavelengths are available as light sources (755, 816 and 850 nm). The emitted pulses of the laser diodes have a repetition of 9 MHz for each wavelength. The photons reach a depth of several centimetres with a passing through of the scalp, skull and frontal lobe.[7] Details of methodology has already been described elsewhere.[7,9]

The absorption coefficients are used to determine the concentration of oxygenated haemoglobin and deoxygenated haemoglobin.[9,14] Out of oxygenated and deoxygenated haemoglobin, Hb_{tot} can be calculated by the following equation[9]:

$$\text{Hbtot} = \text{oxygenated} + \text{deoxygenated haemoglobin}$$

Time-resolved NIRS measurements enables absolute values of CBV. It can be calculated by using the Hb_{tot}, the factor 0.89, representing the cerebral-to-large vessel haematocrit ratio and the concentration of haemoglobin in the blood[7,9,15,16] using the equation:

$$\text{CBV}\left(\frac{\text{mL}}{100\text{g}}\right) = \frac{\text{Hbtot x } 0.89}{\text{Hb concentration in the blood}}$$

2.3 | Measurement protocol

Five time-resolved NIRS measurements were performed each for 1 min in each neonate. The source-detection separation was 3 cm, and the sensors were fixated on a probe pad. The NIRS sensors was placed on the left frontotemporal lobe using an adhesive tape for a single measurement. Then the sensor was removed and after 20-second rest period, the sensor was replicated at the approximately same location. This procedure was conducted in total for five times. Absolute values of CBV were recorded. All variables were stored with a sampling rate of 8 s (0.13 Hz) continuously in a multichannel system 'alpha-trace digital MM' (Best Medical Systems, Vienna, Austria) for subsequent analysis.

2.4 | Statistical analysis

This was a secondary outcome analysis. A precision analysis of cerebral oxygen saturation using the same study population and study protocol for analysis has already been published by Avian et al.[9] The sample size estimation in Avian et al.[9] was performed to analyse the precision of cerebral oxygen saturation obtained by time-resolved NIRS measurements. Sample size calculation was performed using 95% confidence intervals for the precision of measurement of cerebral oxygen saturation. The precision of measurements of cerebral oxygen saturation can be defined as the variation of consecutive measurements. Sorensen and Greisen[13] observed a within-patient variation of 5.2% when re-siting the sensors. In line with this result a difference of 5% was defined as clinically relevant difference. Therefore, our sample size calculation was based on an upper limit of the 95% confidence interval of the precision of 5%. According to the algorithm of Hopkins[17,18] 65 neonates had to be included to get an upper limit of the 95% confidence interval of 5% when the precision is 4.5% and five reapplications of the sensors are performed. Considering a dropout rate of 10% 73 neonates had to be included.

For calculating the precision of CBV measurement, a variance component analysis was conducted to quantify the factors influencing the variability in CBV values. Therefore, a mixed effects model with random effect (patient), fixed effects (reapplication, single application, interaction of reapplication*single application) and CBV as a dependent variable was used. A minimum norm quadratic unbiased estimation model with unit a priori values for the ratios of the variance components to the residual's variance and the residual itself was chosen. Resulting variance components were transferred to percentages of the whole variance. Furthermore, the root square of the variance components was calculated to get a parameter to quantify the variation. The within-patient variation was reported to describe the precision of the measurement. For calculating a descriptive measure of the observed variation of the measurement, the deviation of the observed CBV values to the individual mean was calculated (CBV). 2.5% and 97.5% percentile scores for these deviations with associated 95% confidence intervals using bootstrapping technique were calculated. The used bootstrapping algorithm draws 1000 samples using simple bootstrap resampling. 95% confidence intervals were calculated using the percentile method. Analyses were conducted with no imputation for any missing data. In the analysed outcome (CBV) 2.7% missing values occurred. Statistical analysis was performed using IBM SPSS Statistics version 24 (IBM Corp, New York, USA).

TABLE 1 Demographic and clinical characteristics of the included neonates [mean ± SD, median (IQR) or *n* (%)].

	Preterm neonates *N* = 70
Age, days	4.7 ± 2.0
Sex (female/male)	33 (47)/37 (53)
Gestational age, weeks	33.4 ± 1.7
Weight (birth), g	1931 ± 398
Weight (measurement), g	1876 ± 388
Apgar 1	8 (7–9)
Apgar 5	9 (8–10)
Apgar 10	9 (9–10)
CBV, mL/100 g brain	1.85 ± 0.30
Total haemoglobin, μmol	45.2 ± 8.5

Abbreviation: CBV, cerebral blood volume.

3 | RESULTS

Between October 2017 and August 2018, 73 preterm neonates were enrolled to the prospective observational study. Three neonates (4%) were excluded due to incomplete data. The descriptive data of the remaining 70 neonates are displayed in Table 1. Mean Hb_{tot} was 45.2 ± 8.5 μmol and showed a slight increase with gestational age ($r = 0.254$, $p = 0.034$). Conducting five reapplications, each resulting in at least seven NIRS values per 1 min measurement period, resulted in maximum of 2450 possible values for each parameter. For CBV 67 missing values were observed. Overall mean for the remaining 2383 CBV values was 1.85 ± 0.30 mL/100 g brain (coefficient of variation: 0.161). Looking on each reapplication separately the individual mean values for all five measured values were 1.86 ± 0.32 mL/100 g brain (application 1), 1.84 ± 0.26 mL/100 g brain (application 2), 1.85 ± 0.31 mL/100 g brain (application 3), 1.86 ± 0.29 mL/100 g brain (application 4) and 1.83 ± 0.31 mL/100 g brain (application 5) (Figure S1). 95% of the measured CBV values varied in a range from −0.31 to 0.33 from the overall individual mean. Taking the deviation of the mean of each single application for each patient, this range reduced to −0.07 to 0.07 mL/100 g brain (Table 2, Figure 1). In CBV variance components that could be assigned to differences between patients represented 65.2% of the total variance. Further 32.6% could be assigned to differences between reapplications, 0.0% to differences within one single application and 2.2% to different changes within applications (Table 3). The precision of the measurement, defined as within-variation in CBV, was 0.24 mL/100 g brain. The placement-replacement variability was 0.17 mL/100 g brain.

TABLE 2 Observed deviation of each measurement from the individual overall mean and mean of each application.

	Deviation from			
	Overall mean		Mean of each single application	
	2.5% percentile (95% CI)	97.5% percentile (95% CI)	2.5% percentile (95% CI)	97.5% percentile (95% CI)
CBV, mL/100 g brain	−0.314 (−0.340 to −0.283)	0.329 (0.316 to 0.360)	−0.071 (−0.071 to −0.714)	0.071 (0.071 to 0.086)

Abbreviation: CBV, cerebral blood volume.

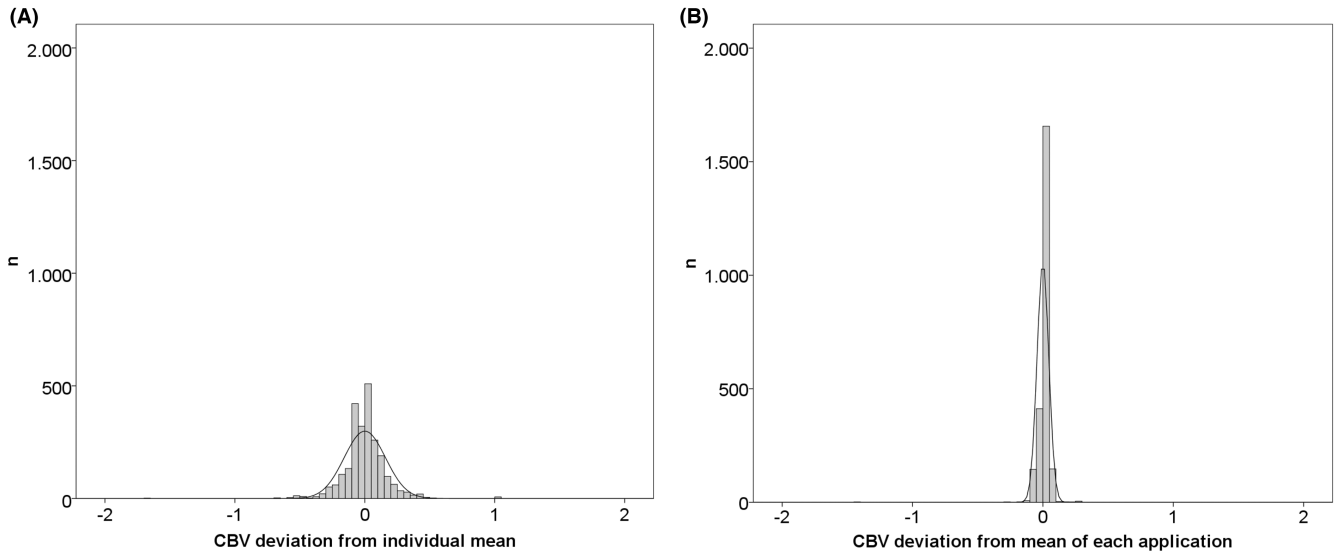

FIGURE 1 Distribution of the deviation of each measurement from (A) the individual overall mean and (B) the mean of each application. Cerebral blood volume is presented in mL/100 g brain.

TABLE 3 Absolute and relative variance components of patients, reapplication and single application. Results are based on a mixed effects model with random effect (patient) and fixed effects (reapplication, single application). Resulting variance components were transferred to percentages of the whole variance to show the proportion of the variance that is due to (A) the differences between patients, (B) reapplications, (C) differences within a single application and (D) differences in the changes within a single application between reapplications (interaction).

	Variance components			
	Patient	Reapplication	Single application	Interaction of reapplication*single application
CBV	0.058 (65.2%)	0.029 (32.6%)	0.000 (0.0%)	0.002 (2.2%)

Abbreviation: CBV, cerebral blood volume.

4 | DISCUSSION

This study investigated CBV in stable preterm neonates using time-resolved NIRS. The precision of CBV measured by performing five measurements in succession, was further analysed. We observed an overall mean in CBV of 1.85 ± 0.30 mL/100 g brain with a within-variation for CBV of 0.24 mL/100 g brain, which can be described as precise. Further, the coefficient of variation was 0.16, whereby the coefficient of variation can only be interpreted to a limited extent due to the lack of proportionality between the standard deviation and the mean. Furthermore, 95% of the measured CBV values varied in a range from −0.31 to 0.33 mL/100 g brain. The majority of the variation was difference due to the patients, whereby approximately a third of the total variance was differences between reapplications. These results were in accordance with a recently published work by Avian et al.[9] with the same study design and the same cohort of patients. They investigated the precision of cerebral oxygen saturation obtained by time-resolved NIRS measurements and observed a within-patient precision of 2.6%, which was also defined as precise. Further, Hb_{tot}, an important parameter, displaying oxygenation in the brain, was observed by Avian et al.[9] A precision of 7.5 µmol for Hb_{tot} was reported with an overall mean of Hb_{tot} of 45.2 ± 8.5 µmol.

The accuracy of the recorded values becomes paramount when evaluating the precision of pulse oximetry, which serves as the primary device for monitoring of arterial oxygen saturation. Various

manufacturers may exhibit differences in the accuracy of their devices. Typically, within the arterial oxygen saturation target ranges for neonates, it has been reported that a standard deviation of 2% and, consequently, an error of up to 4% in pulse oximetry can be observed.[19]

The precision required for achieving reproducible measurements holds clinical significance, due to the need of distinguishing normal from pathological conditions. Sorensen and Greisen[13] investigated the precision of cerebral tissue oxygenation index measured with the NIRO 300. They described low precision with a wide within-variation if one single measurement was performed. Whereby, reapplications, in this study five to eight reapplications in a time period of 15 to 25 min, increased reproducibility to a within-variation that was comparable to the precision of pulse oximetry. Lower precision of one single measurement may be due to physiological variation in arterial oxygen saturation or cerebral blood flow, movement artefacts, measurement errors, gyral geometry and presence of hair. Reapplications can minimise these factors, which further results in higher precision.[13] Menke et al.[20] investigated the reproducibility of cerebral oxygen saturation measured by 20 reapplications, with a duration of 30 s each and a one-minute interval in between the measurements. They observed a good reproducibility of cerebral oxygen saturation, whereby other NIRS parameters including oxygenated haemoglobin, deoxygenated haemoglobin and Hb_{tot} were less reproducible. These variations were assumed as a result of reapplications. In the study of Menke et al.,[20] CBV was observed. Nevertheless, as CBV is in correlation with Hb_{tot}, the observed results may also influence CBV.

A range of five to 20 reapplications were executed in the studies by Sorensen and Greisen[13] and Menke et al.[20] These amount of reapplications are associated with a greater expenditure of time which is, in many cases, not feasible in clinical routine. Besides being cumbersome in clinical practice, reapplications performed over a time period of 15 to 20 min are prone to errors due to physiological changes, even in stable neonates.

Physiological changes cannot be minimised by reapplications. These changes can only be observed in continuous monitoring over a longer period of time. Therefore, in situations of rapid changing haemodynamic situations, reapplications to not provide any advantages. This is particularly relevant during the first few minutes after birth, during the initial transition from the fetal-to-neonatal stage, when enormous changes in CBV occur due to physiological changes in cardiovascular and respiratory system.[1] The time immediately after birth and changes in cerebral and peripheral haemodynamic in this transition period, have a great influence on CBV. Schwaberger et al.[1] observed a decrease in ΔCBV within the first 15 min after birth, which is also influenced by a rise in pO_2 and a decrease of pCO_2 levels during initial postnatal transition period. This is in accordance with Morimoto et al.[21] They investigated absolute values of CBV in vaginally born term neonates also using time-resolved NIRS. These findings showed a course of CBV comparable to described values by Schwaberger et al.[1]: CBV decreases during immediate fetal-to-neonatal transition period. Fujioka et al.[8] also investigated changes of CBV over time. The authors described changes in CBV during the first 3 days after birth in term and preterm neonates, using the NIR-TRS system. They observed almost no changes in CBV after the first 24 to 72 h after birth in term neonates, whereby in preterm neonates, an increase after the first 12 to 48 h after birth was observed and after 48 h only slight changes were noticed. A comparable course of CBV within the first 3 days after birth was also described by Ishii et al.[22] Beside postnatal age, gestational age further influences CBV. The difference of CBV in preterm and term neonates has already been investigated and is mainly influenced by differences in maturation of cerebral vessels and difference in sensibility to changes of metabolism including pCO_2 and pO_2.[8,23] CBV values were significantly higher in term neonates compared to preterm neonates within the first 3 days after birth.[8] Various studies have described CBV values in a similar time period compared to the present study, where CBV was measured at a mean of 4.7 ± 2.0 days after birth. In our present study, the mean CBV was 1.85 ± 0.30 mL/100 g brain. This is comparable to measurements performed within the first 3 days after birth in preterm neonates (1.97 ± 0.33 mL/100 g brain), but showed a difference to CBV in term neonates (2.45 ± 0.47 mL/100 g).[8] Ishii et al.[22] also investigated CBV in moderate-to-late-preterm neonates during the first 3 days after birth and describe comparable CBV values (approximately 2 mL/100 g brain). Slightly higher CBV values were described by Wyatt et al.[15] (2.22 mL/100 g brain) in neonates born 25 to 40 weeks of gestation in a measurement period of 4 to 240 h after birth. The difference of these results to the results of our present study may be explained by the fact of the great variation in gestational age. In contrast to all data, Baenzinger et al.[24] investigated CBV values of approximately 6 mL/100 g brain in preterm neonates at 4 and 24 h after birth. Their results were well above values described so far and have to be interpreted with caution. As our results are comparable to other published values,[8,22] CBV values of our present study (1.85 ± 0.30 mL/100 g brain) may be interpreted as normal values of stable moderate-to-late-preterm neonates on the fourth day after birth using the time-resolved NIRS technique, which has a high measurement accuracy.

In literature, CBV is described to be taken as a surrogate measure of cerebral haemodynamics, as it is related to cerebral blood flow and central venous pressure.[1,25–27] Cerebral blood flow is controlled by both cerebral perfusion pressure and cerebrovascular resistance.[25] Further, studies have indicated an increase in CBV following the obstruction of the jugular vein.[26,27]

Cerebral blood volume is a complex physiological concept, as there are arterial, capillary and venous components, whereby the ratio of arterial to venous is estimated to 25:75.[28] The arterial to venous ratio is further influenced by oxygen delivery and oxygen consumption. In normal conditions, with intact cerebral autoregulation and measurements in small vessels with a diameter of <0.1 mm, oxygen delivery reflects the constant variable. Oxygen consumption changes depending on the condition.[25,28] Large

vessels alter signal quality and oxygen consumption, which has an impact on the measured CBV and must be taken into account in the interpretation.

Beside continuous beside NIRS measurements, trend-monitoring of estimated CBV can be performed with Doppler ultrasound measurements of cerebral blood flow.[29,30] Nevertheless, this method may only allow the estimated CBV and allows to monitor changes in CBV, leading to limited usability in clinical routine. Advantages of NIRS measurements comparable to other techniques for CBV measurements show better availability and easier handling in terms of measurement. The latter, especially, with regard to non-invasive measurements with low examination costs and shorter duration of measurement.

As mentioned before, CBV reflects cerebral perfusion and provides important additional information about cerebral haemodynamic processes. In asphyxiated neonates after hypothermia, during rewarming phase, CBV increases, which might be a result of reperfusion.[31] Further, Nakamura et al.[32] compared CBV in neonates with hypoxic–ischemic encephalopathy and hypothermic therapy to those without hypothermic therapy. They observed higher CBV within the first 24 h after birth in neonates with hypoxic–ischemic encephalopathy and with adverse outcome compared to neonates with age-appropriate-outcome.

The above mentioned studies reflect the vulnerability of CBV in different physiological or pathophysiological conditions and further the potential of CBV to provide additional information. Alterations in CBV may be of great importance especially in premature born neonates, with high risk for cerebral brain injury, including cerebral haemorrhage.

The present study has limitations: First, the tNIRS-1 has a measurement cycle for cerebral oxygen saturation of 5 s and further allows the calculation of Hb_{tot} each five-second period. Comparing this with other devices, it is slower. Second, the optical homogeneity of the tissue under the optode is uncertain, which may influence the results. Third, not all details about data analysis including time window and censoring of 'unlikely' values are known. Both factors are likely to influence results. The strength of this study is the amount of CBV values for final analysis.

5 | CONCLUSION

CBV in stable preterm neonates was 1.85 ± 0.30 mL/100 g brain using time-resolved NIRS measurements. Measurements were performed by five reapplication and provided a within-variation in CBV of 0.24 mL/100 g brain. Based on the accuracy of the device and precision obtained by our data, the overall mean CBV of 1.85 ± 0.30 mL/100 g brain, may be assumed as normal value for this cohort.Considering the results of this present study and the precision of cerebral oxygen saturation using the tNIRS-1,[9] it can be assumed that five reapplications by the tNIRS-1 using the time-resolved technique, provide precise results with a procedure that is feasible in clinical routine.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the parents for giving consent to investigate their infants, as well as all the midwives, nurses and physicians involved in the treatment of these neonates. Further we want to thank Wataru Kamadu, Hamamatsu Photonics K.K., Japan, for this technical support. We also would like to thank Evelyn Ziehenberger for her assistance in completing this study.

FUNDING INFORMATION

This study did not receive any specific funding.

CONFLICT OF INTEREST STATEMENT

M.W. is a president of the board and co-founder of OxyPrem AG. No further financial and other conflicts of interest to disclose.

ETHICS STATEMENT

The study was approved by the Regional Committee on Biomedical Research Ethics of the Medical University of Graz (EC-Number: 29-351 ex 16/17), and written informed consent was obtained from the parents before inclusion into the study.

ORCID

Christina Helene Wolfsberger https://orcid.org/0000-0002-9770-3487
Gerhard Pichler https://orcid.org/0000-0003-2405-7143
Berndt Urlesberger https://orcid.org/0000-0003-0648-5785

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wolfsberger CH, Avian A, Schwaberger B, Pichler G, Wolf M, Urlesberger B. Precision and normal values of cerebral blood volume in preterm neonates using time-resolved near-infrared spectroscopy. Acta Paediatr. 2023;00:1–7. https://doi.org/10.1111/apa.17040