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CLINICAL RESEARCH ARTICLE

Regional splanchnic oxygen saturation for preterm infants in the first week after birth: reference values

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BACKGROUND: Near-infrared spectroscopy is used in the assessment of regional splanchnic oxygen saturation (r_sSO_2), but solid reference values are scarce. We aimed to establish reference values of r_sSO_2 for preterm infants during the first week after birth, both crude and modeled based on predictors.

METHODS: We included infants with gestational age (GA) <32 weeks and/or birth weight <1200 g. We excluded infants who developed necrotizing enterocolitis or sepsis or who died. In the first week after birth, we determined a daily 2-h mean of r_sSO_2 to assess its associations with sex, GA, postnatal age (PNA), small-for-gestational age (SGA) status, patent ductus arteriosus, hemoglobin, nutrition, and head circumference at birth and translated those into a prediction model.

RESULTS: We included 220 infants. On day 1, the mean ± SD r_sSO_2 value was 48.2% ± 16.6. The nadir of r_sSO_2 was on day 4 (38.7% ± 16.6 smoothed line) to 5 (37.4%±17.3, actual data), after which r_sSO_2 increased to 44.2% ± 16.6 on day 7. The final model of the reference values of r_sSO_2 included the following coefficients: $r_sSO_2 = 3.2 - 7.0 \times PNA + 0.8 \times PNA^2 - 4.0 \times SGA + 1.8 \times GA$.

CONCLUSIONS: We established reference values of r_sSO_2 for preterm infants during the first week after birth. GA, PNA, and SGA affect these values and need to be taken into account.

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IMPACT:

- Regional splanchnic oxygen saturation is lower in infants with a lower gestational age and in small-for-gestational age infants.
- Regional splanchnic oxygen saturation decreases with a higher postnatal age until day 4 after birth and then increases until day 7 after birth.
- Gestational age, postnatal age, and small-for-gestational age status affect regional splanchnic oxygen saturation and need to be taken into account when interpreting regional splanchnic oxygen saturations using NIRS.
- Reference values for infant regional splanchnic oxygen saturation can be computed with a formula based on these variables, as provided by this study.

INTRODUCTION

At the neonatal intensive care unit (NICU), preterm infants are hospitalized for long periods with risk of severe complications and life-threatening events.[1,2] To ensure successful treatment and early diagnosis of these complications, various monitoring tools have been introduced to assess individual physiological functioning at the NICU. Near-infrared spectroscopy (NIRS) is such a tool. This non-invasive technique uses near-infrared light to distinguish oxygenated from deoxygenated hemoglobin. Biological tissues are relatively transparent to near-infrared light and this light is absorbed by molecules such as hemoglobin. Based on this, NIRS measures the regional oxygen saturation of the underlying tissue.[3] As NIRS measures a tissue vascular bed that mostly contains venous blood, NIRS values result from a balance between arterial oxygen supply and tissue oxygen use. NIRS can, therefore, be used to identify organs at risk of tissue hypoxia.[4]

In preterm infants, the intestines are frequently exposed to episodes of hypoxia, which has been associated with feeding intolerance and necrotizing enterocolitis.[5–8] Therefore, a diagnostic and prognostic use of regional splanchnic oxygen saturation (r_sSO_2) monitoring has been suggested. R_sSO_2 has also been studied to guide nutritional management, to investigate the effect of anemia and blood transfusions, and to examine the effect of various medications such as ibuprofen on splanchnic oxygenation.[9–15] However, the use of r_sSO_2 in clinical care is currently limited, in part due to a lack of solid reference values.[16,17] Only a few studies in small samples are available as basis for the current reference values. These values suggest that r_sSO_2 is associated with gestational age (GA) and postnatal age (PNA). However, r_sSO_2

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may differ between monitors. In order to optimize the use of r_sSO_2, we aimed to establish reference values of r_sSO_2 using INVOS 5100c monitors with neonatal sensors for preterm infants during the first week after birth, both crude and modeled based on predictors.

METHODS

Patient population

In this observational cohort study, we included all infants with a GA <32 weeks and/or a birth weight (BW) <1200 g who were admitted to our NICU in the first week after birth between January 2016 and December 2017. Infants were excluded in case of chromosomal or congenital abnormalities and gastrointestinal diseases such as volvulus and spontaneous intestinal perforation. Infants with necrotizing enterocolitis (Bell's stage ≥2)[18] were also excluded because of the association of r_sSO_2 in the first week after birth and subsequent development of necrotizing enterocolitis.[7,19] Data from infants who developed clinical sepsis (sepsis symptoms with a positive blood culture and/or C-reactive protein >20 mg/L) were excluded from 1 day prior to diagnosis and all subsequent days because intestinal perfusion has been shown to be different during these days in these infants.[20] In case an infant died, data from that day were excluded. The medical ethical committee of the University Medical Center Groningen approved this study.

Data collection

As part of standard clinical care, we measured r_sSO_2 during the first week after birth for at least 2–3 times a day for a minimum of 2 h using an INVOS 5100c monitor (INVOS™ 5100C [Medtronic, Dublin, Ireland]). The neonatal INVOS™ SomaSensor was placed infraumbilically, on top of Mepitel® sheets (Mölnlycke, Sweden) to protect the skin. R_sSO_2 measurements were halted if infants had an umbilical catheter taped to the infraumbilical skin or during infraumbilical skin irritation. R_sSO_2 values were saved in an offline pseudonymized database every 5 s.

Sensor placement was checked by the attending nurse and verified every morning by a researcher. We calculated a daily 2-h mean of r_sSO_2 before or, when unavailable, closest to the sensor verification. We selected a 2-h period with at least 80% of available data. Artifacts were manually removed and defined as misplacement of the sensor, unexplained sudden non-physiological change of the values, or a lack of physiological variability of the values, again indicating sensor misplacement. Regional cerebral oxygen saturation (r_cSO_2) was simultaneously measured on the left or right frontoparietal side of the head and calculated in the same period and with an identical procedure as r_sSO_2. Peripheral arterial oxygen saturation (SpO_2) was simultaneously measured using Nellcor® pulse oximeters (Medtronic, Dublin, Ireland), with target range 90–92% and alarm settings at 86 and 93% in case of oxygen therapy.

We further collected data on pregnancy, birth, and the early neonatal period from the hospital records. Data on pregnancy regarded multiple gestation, parity, and mode of delivery. Data on birth regarded BW, small-for-gestational age (SGA) status defined as <p10 according to Dutch reference values,[21] GA, sex, head circumference at birth (converted to *Z*-scores according to Niklasson),[22] and Apgar scores at 1 and 5 min. Data on the early neonatal period regarded SNAPPE-II score[23]; periventricular or intraventricular hemorrhage present in the first week after birth categorized according to the modified Papile classification[24]; patent ductus arteriosus (PDA) (categorized as no clinical signs of PDA/not assessed and no PDA after echocardiographic assessment, non-hemodynamic significant PDA, and hemodynamic significant PDA (hsPDA) that needed treatment); daily weight *Z*-scores according to Dutch reference values[21]; type of nutrition (categorized as ≥50% mother's milk, <50% mother's milk, or nil by mouth); and hemoglobin level for a period from 12 h before to 12 h after the r_sSO_2 measurement.

Data handling and statistical analyses

To allow making valid and efficient inferences, missing r_sSO_2 values were imputed.[25] We imputed the missing r_sSO_2 values using predictive mean matching[26] based on the following variables: GA, SNAPPE-II score as measure of disease severity, daily weight, SpO_2, previous and future r_sSO_2 values, r_cSO_2, and hemoglobin levels. For the imputed values based on these variables, we further assumed no dependency on other variables, i.e., further missingness at random. Missing values were assessed by a repetitive total of 20 imputations, and all analyses were based on the pooled results of these imputations.

Mean r_sSO_2 values were graphically presented for the first week after birth and aberrant r_sSO_2 values were indicated as higher or lower than one standard deviation. We present the data of r_sSO_2 with a "smoothed" line. In this line, the measurement error per measurement is reduced by taking into account the adjacent measurements on the same child, enabling a more precise estimate of patterns. Because of this reduction in random errors, smoothed estimates may slightly vary from observed ones.

We also calculated the mean and SD of the actual measured r_sSO_2 values for each day and determined on which day the nadir occurred. Statistical differences of r_sSO_2 between various days were tested using Student's *t* test and are presented in a Supplemental Table.

Next, we constructed a model to predict the course of the r_sSO_2 during the first week. To this end, we assessed associations of r_sSO_2 with PNA (in days after birth), sex (male/female), GA (weeks), SGA (yes/no), PDA (yes/no), hemoglobin level, nutrition (≥50% mother's milk yes/no), and head circumference *Z*-score at birth according to GA, using multilevel models (due to the longitudinal study design). As first step, we determined the linear as well as quadratic effect of PNA to determine the best model using goodness-of-fit criteria.[27] Next we assessed the associations of r_sSO_2 with all individual variables separately, only adjusting for PNA. Subsequently all variables with a P value < 0.1 were included into a multivariable model. We then reduced this multivariable model to a final prediction model using a backward elimination procedure, with variables eliminated based on $P < 0.05$.

To validate our final model, we performed a post hoc power analysis using a simulation-based approach with Monte Carlo facilities regarding the detection of the quadratic growth with covariates.[28] This power analysis, performed over the 20 imputations, showed that the current study had a power of at least 90% to detect the type of growth, i.e., course of r_sSO_2 during the first 7 days, in analogy to growth curves (linear and quadratic) and the associations with GA and SGA. This shows that our study had adequate power to reject the null hypothesis of zero correlation.

We used IBM SPSS Statistics 23 (IBM Corp., Armonk, NY), SAS version 9.2 (SAS Institute INC., Cary, NC), and Mplus version 8.4 (Muthen and Muthen, Los Angeles, CA) for imputation, multilevel analysis, and power analysis, respectively. GraphPad Prism 7.02 (GraphPad Software Inc., La Jolla, CA) was used for graphical displays.

RESULTS

Patient population

Out of 278 infants, we excluded 58 infants because of chromosomal abnormalities ($n = 10$), gastrointestinal diseases including necrotizing enterocolitis ($n = 37$), congenital heart defects ($n = 3$), sepsis ($n = 7$), death on day of birth ($n = 1$), or combinations of these. Patient characteristics are shown in Table 1. Of the 220 included infants, 50 infants had r_sSO_2 measurements on all 7 days, while for 41 infants we imputed r_sSO_2 values on all 7 days. For the remaining 129 infants, r_sSO_2 values were partly

Table 1. Patient characteristics.

	Total ($n = 220$)
Male, *n* (%)	124 (56)
Birth weight (g)	1335 ± 369
Head circumference (cm)	27.0 ± 2.5
Gestational age (weeks)	29.4 ± 2.0
Apgar score 1 min	5.7 ± 2.4
Apgar score 5 min	7.5 ± 1.4
Cesarean section, *n* (%)	129 (59)
Patent ductus arteriosus, *n* (%)	
No patent ductus arteriosus	151 (68)
Not hemodynamic significant	19 (9)
Hemodynamic significant	49 (22)
Unknown	1 (1)
Periventricular–intraventricular hemorrhage, *n* (%)	
None	150 (68)
Grade I/II	48 (22)
Grade III/IV	16 (7)
Unknown	6 (3)
Primiparae, *n* (%)	144 (66)
Multiple births, *n* (%)	
Singletons	157 (71)
Twins	57 (26)
Triplets	6 (3)
Small-for-gestational age, *n* (%)	51 (23)
SpO_2 (%)[a]	
Day 1 after birth	93.6 ± 4.1
Day 2 after birth	94.0 ± 3.6
Day 3 after birth	93.9 ± 3.3
Day 4 after birth	94.6 ± 3.2
Day 5 after birth	95.0 ± 3.4
Day 6 after birth	95.3 ± 3.3
Day 7 after birth	95.2 ± 3.5
Hemoglobin (mmol/L)[b]	
Day 1 after birth	10.3 ± 1.8
Day 2 after birth	9.6 ± 1.8
Day 3 after birth	10.0 ± 1.6
Day 4 after birth	9.6 ± 1.8
Day 5 after birth	9.4 ± 1.7
Day 6 after birth	9.3 ± 1.6
Day 7 after birth	8.9 ± 1.6
Nutrition, ≥50% mother's milk (%)[c]	
Day 1 after birth	62 (28)
Day 2 after birth	79 (37)
Day 3 after birth	103 (50)
Day 4 after birth	141 (72)
Day 5 after birth	156 (82)
Day 6 after birth	156 (84)
Day 7 after birth	150 (86)
Mortality, *n* (%)[d]	11 (5)

Data are expressed as mean ± standard deviation or as number (percentage).
[a]Number of infants used for analysis (day 1: $n = 202$, day 2: $n = 201$, day 3: $n = 193$, day 4: $n = 183$, day 5: $n = 173$, day 6: $n = 164$, day 7: $n = 149$).
[b]Number of infants used for analysis (day 1: $n = 142$, day 2: $n = 113$, day 3: $n = 131$, day 4: $n = 106$, day 5: $n = 90$, day 6: $n = 85$, day 7: $n = 67$).
[c]Number of infants used for analysis (day 1: $n = 220$, day 2: $n = 216$, day 3: $n = 206$, day 4: $n = 196$, day 5: $n = 190$, day 6: $n = 185$, day 7: $n = 174$).
[d]Deceased within the first week after birth.

imputed. Reasons for missing values were presence of an infraumbilical taped umbilical catheter, the attending doctors' preference to remove the sensor for unknown reason, death between day 2 and 7 after birth, sepsis between day 3 and day 7 after birth, discharge from NICU, no NIRS device available, artifacts and insufficient NIRS data, or an unknown cause (Supplemental Table S1).

Reference values for r_sSO_2

On the first day after birth, the mean (±SD) r_sSO_2 value was 48.2% (±16.6). Mean r_sSO_2 decreased during the first days after birth. For the smoothed line, the nadir of r_sSO_2 was on day 4 (38.7% ± 16.6), after which the mean r_sSO_2 increased to 44.2% (±16.6) on day 7 (Fig. 1). In Supplemental Fig. S1, we present the curve for the 50 infants with measurements on all days. Of note, mean SpO_2 levels ranged between 93.6 and 95.3% during the first 7 days after birth (Table 1). In Supplemental Table S2, we present the mean (±SD) of the actual measured r_sSO_2 values for each day, including the statistical significance of differences between various days. The nadir was now on day 5 (37.4% ± 17.3).

For the prediction model, we first assessed the associations of GA, SGA, PDA, hemoglobin level, nutrition, and head circumference at birth with r_sSO_2, only adjusted for PNA and PNA-squared. This showed that PNA, GA, SGA, PDA, and head circumference at birth were associated with r_sSO_2 at $P < 0.1$ (Table 2). Next, we entered these variables in a multivariable model, which we reduced to a final prediction model by using a backward elimination procedure. This yielded that PNA, GA, and SGA remained significantly associated with r_sSO_2 (Table 3). This resulted in the formula: $r_sSO_2 = 3.2 - 7.0 \times PNA_{(i)} + 0.8 \times PNA^2{}_{(i)} - 4.0 \times SGA + 1.8 \times GA$ (i = day 1–7, GA: weeks, SGA: 0 = No, 1 = Yes). Additional information of all studied variables for the prediction model can be found in Supplemental Table S3. This formula represents that, up to the fourth day after birth, mean r_sSO_2 values decline and then increase toward day 7 after birth. Furthermore, mean r_sSO_2 values were lower for infants with a lower GA and for infants who were SGA (Fig. 2).

DISCUSSION

In this study, we established reference values of r_sSO_2 for preterm infants during the first week after birth. GA, PNA, and SGA affected these values and need to be taken into account when interpreting r_sSO_2 using NIRS.

In this study, r_sSO_2 decreased from day 1 after birth until day 4 after which r_sSO_2 increased with increasing PNA until day 7 after birth. These results mostly confirm the findings by McNeill et al. and Cortez et al. regarding the first week after birth[16,17] but now in

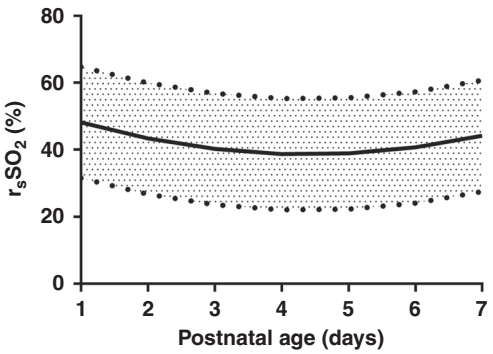

Fig. 1 Mean (+/−1SD) regional splanchnic oxygen saturation**.** The black line is the mean value of regional splanchnic oxygen saturation during the first week after birth. The dotted line represents one standard deviation from the mean. R_sSO_2 regional splanchnic oxygen saturation.

Table 2. Estimates of a multilevel regression model of regional intestinal oxygen saturation (as dependent variable) and clinical variables, adjusted for postnatal age.

Clinical variables	Estimates	CI	
		Lower limit	Upper limit
Gestational age (weeks)	1.72‡	0.88	2.56
Gender (male ref. category)	0.34	−2.73	3.41
Head circumference (*Z*-score)	1.51*	−0.06	3.07
Hemoglobin (mmol/L)	0.03	−1.03	1.09
No PDA (ref. category)			
Non-hsPDA	−2.60	−8.22	3.03
HsPDA	−5.37†	−9.19	−1.55
Nutrition (no feedings) (ref. category)			
Nutrition (<50% mother's milk)	0.07	−3.84	3.99
Nutrition (≥50% mother's milk)	−2.17	−6.33	1.98
Small-for-gestational age	−3.53*	−7.37	0.32

PDA patent ductus arteriosus, *HsPDA* hemodynamic significant patent ductus arteriosus, *CI* confidence interval.
*P value < 0.1; †P value < 0.01; ‡P value < 0.001.

Table 3. Result of the final multilevel regression model of regional intestinal saturation (as dependent variable) and clinical variables: final model based on backward elimination procedures.

Clinical variables	Estimates	CI	
		Lower limit	Upper limit
Intercept	3.24	−21.11	27.60
Postnatal age (linear)	−7.0‡	−9.01	−4.98
Postnatal age (quadratic)	0.77‡	0.45	1.10
Gestational age	1.77‡	0.93	2.60
Small-for-gestational age	−3.99**	−7.68	−0.29

CI confidence interval.
**P value < 0.05; ‡P value < 0.001.

a considerably larger sample with more precise estimates. Our results contrast those of Patel et al. who found a different course of r_sSO_2, i.e., an increase of r_sSO_2 until day 3, after which r_sSO_2 decreased until day 7 after birth.[7] This different course could be explained by the fact that Patel et al. used another site of placing their sensors, i.e., right lower abdomen, whereas we measured centrally in the infraumbilical region. Furthermore, they prospectively included infants only within the first 24 h after birth. This may have led to bias, by exclusion of the sickest infants as parents may not have been asked informed consent. Finally, they measured r_sSO_2 for only 5 min during a "steady state" without episodes of apnea, bradycardia, or arterial oxygen desaturation, which may occur frequently in the first days after birth and may have resulted in a lower r_sSO_2 in our study.[7] Therefore, our results may better represent all preterm infants admitted to the NICU, resulting in a nadir on day 4.

We found several variables to be associated with r_sSO_2 for preterm infants in the first week after birth, modeled for predictors. Of these variables, PNA was associated with r_sSO_2 and a lower GA was associated with lower r_sSO_2 values as has been demonstrated before.[16,17] This study adds that SGA was also associated with lower r_sSO_2 values. We did not find any associations between r_sSO_2 and sex and hemoglobin level as showed before.[16,17] Similarly, this study demonstrated that

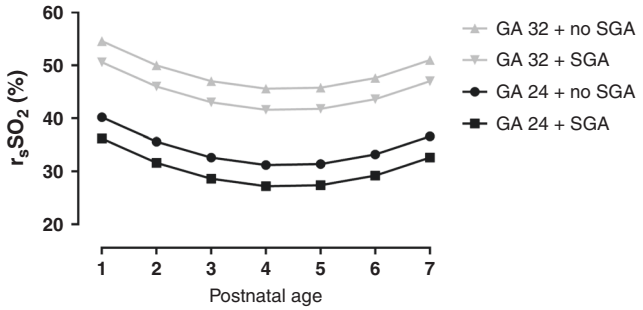

Fig. 2 Mean regional splanchnic oxygen saturation of different groups of infants**.** The course of mean regional splanchnic oxygen saturation of 4 subgroups of infants, illustrating differences between infants born at 24 and 32 weeks, with and without SGA. Regression coefficients of GA and SGA status are presented in Table 3. R_sSO_2 regional splanchnic oxygen saturation, GA gestational age, SGA small-for-gestational age.

confirmed hsPDA, nutrition, and head circumference *Z*-score at birth were not associated with r_sSO_2. In contrast, McNeill et al. reported a moderate-strength positive association between hemoglobin and r_sSO_2.[16] As r_sSO_2 is expressed as the ratio of oxygenated to total hemoglobin, a positive association between r_sSO_2 and hemoglobin seems plausible. We may not have found this association in our multivariable models, because hemoglobin levels were strictly controlled and therefore did not vary enough to show a significant relation with r_sSO_2.

We found an initial decrease in r_sSO_2 in the first days after birth, followed by an increase from day 5 onwards. This course may be affected by several clinical variables in various degrees. Of these variables, it is known that PDA influences mesenteric hemodynamics of preterm infants.[29,30] Ledo et al. reported the course of r_sSO_2 in the first week of life, stratified for PDA status, and showed an initial decrease until the third day after birth in all groups.[30] A subsequent increase in r_sSO_2 was only observed in infants with closure of the ductus arteriosus, either spontaneously or following treatment with ibuprofen. Thus the initial decrease in r_sSO_2 suggests a maximal effect of the left-to-right ductal shunt after full transition after birth, resulting in decreased mesenteric blood flow.[31–33] With ductal closure within 2–6 days after birth, mesenteric blood flow restores and r_sSO_2 increases.[33] Based on the foregoing, an association between hsPDA and r_sSO_2 could be assumed. In our study, however, we found no association between hsPDA and r_sSO_2 when corrected for other variables. This association may have been suppressed by GA in the final model, as GA is associated with both r_sSO_2 and a higher risk of an hsPDA. Alternatively, hsPDA may have been underdiagnosed during the first week in our cohort.

The initial decrease in r_sSO_2 may also be explained by growth and intestinal maturation processes. Although there are no clinical studies available using simultaneous Doppler and NIRS measurements, an increase in mesenteric blood flow has been observed from birth onwards, while we demonstrated an initial decrease in r_sSO_2, suggesting that oxygen extraction increases to a greater extent than blood flow in the first days after birth. In the absence of PDA, this decrease in r_sSO_2 may be explained by increased intestinal activity, e.g., digestion–absorption in the presence of increasing volumes of enteral nutrition, immunological processes in the presence of the developing microbiome, and intestinal tissue growth.

The question remains why GA and SGA affect r_sSO_2. As NIRS predominantly measures venous hemoglobin, r_sSO_2 represents a balance between arterial oxygen supply and tissue oxygen consumption. The association of SGA with lower r_sSO_2 values may be explained by a lower splanchnic perfusion, as a result of a preferential blood flow to the brain, as seen during and after[34] fetal growth restriction pregnancies often preceding prematurity

and SGA.[35] The association between lower GA and lower r_sSO_2 values suggests that the maturation of the mesenteric vasculature is GA dependent.[16] This is supported by various studies in which abdominal blood flow was demonstrated to increase with increasing GA.[36,37] However, as we did not measure blood flow in our study, we could not confirm this explanation. In tandem, SGA infants and infants with lower GA have the highest need for intestinal growth and development, potentially resulting in an increased oxygen demand. Nevertheless, we propose that the associations of lower GA and SGA with lower r_sSO_2 are mainly a result of reduced intestinal perfusion.

This study on reference values of r_sSO_2 for preterm infants has a number of major strengths, such as having the largest sample to date, collection of data in a clinical care setting, thus representing the actual r_sSO_2 found in preterm infants at the NICU, and the inclusion of various variables to assess associations with r_sSO_2. However, this study has also some limitations. First, we had to impute missing values in several infants on various days. Nevertheless, imputation of missing values, using other related variables to make an assumption of the missing value, is a frequently used and well-accepted method. Moreover, the course of r_sSO_2 was not different after we imputed data compared with only the non-imputed data (data not shown). Second, the broad range of values within one SD suggests to also investigate other aspects of the value, such as variability or relation to cerebral oxygenation. Finally, the reference values found in this study may be dependent on different factors such as the position and type of the sensor, duration of the measurement, type of device, and the SpO_2 value.[38] Nonetheless, although r_sSO_2 values could differ between different units, the associations with PNA, GA, and SGA will probably be consistent between various monitors and sensors.

Our findings imply that clinicians and researchers, when using splanchnic NIRS measurements, have to account for PNA, GA, and SGA status in order to correctly interpret r_sSO_2 values. Furthermore, this study shows that SGA infants and infants with lower GA have lower r_sSO_2 confirming a higher risk of hypoxia of the intestines. In conclusion, these reference values may facilitate identification of infants with aberrant r_sSO_2 values, advance the use of r_sSO_2 monitoring in clinical care, and increase the clinical implication of research results. A next step will be to investigate whether infants developing intestinal diseases such as necrotizing enterocolitis indeed have aberrant r_sSO_2 values compared to preterm infants during the first week after birth.

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AUTHOR CONTRIBUTIONS

M.v.d.H., B.M.D., and E.M.W.K. were involved in the design and execution of the study. R.E.S. contributed to the analysis and interpretation of the data. All other authors were involved in the final consensus process of the protocol and revised the manuscript critically for important intellectual content. M.v.d.H. and B.M.D. drafted the manuscript and all other authors read, edited, and approved the final manuscript for publication.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-01323-3) contains supplementary material, which is available to authorized users.

Competing interests: The authors declare no competing interests.

Consent statement: Due to the retrospective character of the study, no informed consent from the participant's legal guardian was required. Nevertheless, none of the participant's legal guardians objected to participate during admission when they were offered this option.

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