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Evaluation of cerebral oxygenation and perfusion in small for gestational age neonates and neurodevelopmental outcome at 24–36 months of age

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Abstract

Objective: To examine cerebral oxygenation and perfusion in small for gestational age (SGA) compared with appropriate for gestational age (AGA) neonates during the first postnatal week, and to investigate any association with neurodevelopmental outcomes at 24–36 months of age.

Methods: A prospective matched case-control study was conducted evaluating cerebral oxygenation and perfusion, using near-infrared spectroscopy (NIRS), between SGA and AGA neonates, during the first postnatal week. A neurodevelopmental assessment with Bayley-III was performed at 24–36 months of age.

Results: Forty-eight SGA and 48 AGA neonates of similar gestation (32.8 ± 2.1 vs. 32.5 ± 1.9) were enrolled. On the first postnatal day, the cerebral oxygenation was equal between SGA and AGA neonates ($71 \pm 7\%$ vs. $72 \pm 8\%$); however, in the subgroup analysis, males had higher oxygenation compared to female SGA neonates ($73 \pm 7\%$ vs. $69 \pm 7\%$, $P=0.04$). Cerebral perfusion was significantly higher in SGA neonates on the first postnatal day (1.4 ± 0.6 vs. 1.1 ± 0.5 , $P=0.04$), but this difference was diminished on subsequent measurements. There were no significant differences between the SGA and AGA infants regarding the composite cognitive, communication and motor index scores. The length of mechanical ventilation and late-onset sepsis were significant risk factors affecting the cognitive and communication composite index scores, respectively.

Conclusion: Cerebral oxygenation was equal between SGA and AGA neonates, while cerebral perfusion was transiently increased in SGA neonates during the first postnatal day. There was no significant association of cerebral oxygenation and perfusion with neurodevelopmental outcomes.

Keywords: Bayley-III; intrauterine growth restriction; near-infrared spectroscopy.

Introduction

Preterm neonates who are born small for gestational age (SGA) represent a vulnerable group that potentially requires special monitoring and are at increased risk for long-term adverse outcomes [1, 2]. The most popular definition for SGA infants is based on birth weight below the 10th percentile, adjusted for gestational age and gender, using appropriate reference data [3]. In many cases, SGA neonates are caused by intrauterine growth restriction (IUGR), defined by an estimated fetal weight or abdominal circumference below the 10th percentile and the incorporation of the Doppler indices of placental insufficiency or dysfunction [3, 4]. In response to decreased placental blood supply, the fetus redistributes the cardiac output in favour of cerebral blood and nutrient supply, a phenomenon also known as brain-sparing effect [5]. Limited studies have examined the effect of brain-sparing postnatally and the changes of cerebral oxygenation and perfusion in SGA compared to appropriate-for-gestational-age (AGA) neonates [6–8]. Furthermore, limited evidence exists regarding the clinical significance of these early postnatal cerebral changes in the long-term neurodevelopmental outcomes of this preterm neonatal population.

The aim of the current study was to examine cerebral oxygenation and perfusion in a cohort of preterm SGA compared to AGA neonates using near-infrared spectroscopy (NIRS) during the first postnatal week. Furthermore, we sought to investigate any association of the cerebral oxygenation and perfusion parameters, as well as the clinical data, with the long-term neurodevelopmental outcome at 24–36 months of age.

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Materials and methods

Study design

A prospective matched case-control study was conducted from April 2013 to April 2016 in the 2nd NICU of the Aristotle University of Thessaloniki, Greece. The study was approved by the Ethical Committee of the institution and the Aristotle University of Thessaloniki, and a written parental consent was obtained for each neonate prior to the enrolment.

Population

We enrolled neonates of 28–36 weeks' gestation that were SGA and an equal number of matched AGA controls. For each SGA neonate, an AGA control with similar gestation (± 7 days) was enrolled. For the definition of SGA and AGA, we utilised Fenton's growth charts [9]; SGA were neonates with birth weight $< 10^{\text{th}}$ centile for their gestation, while AGA were neonates with a birth weight $\geq 10^{\text{th}}$ and $\leq 90^{\text{th}}$ centile for gestation. Symmetrical SGA were neonates with both birth weight and head circumference $< 10^{\text{th}}$ centile, while asymmetrical SGA were those neonates with birth weight $< 10^{\text{th}}$ and head circumference $\geq 10^{\text{th}}$ centile for their gestation. The population of SGA neonates consisted of the subgroup of neonates that were IUGR based on the *in-utero* estimation of fetal weight or abdominal circumference below the 10th percentile, and the non-IUGR neonates [3].

Neonates in any condition that might potentially influence cerebral oxygenation and perfusion were excluded from the study. Therefore, neonates with congenital central nervous system malformations, congenital cyanotic cardiac disease, hemodynamically significant patent ductus arteriosus, intraventricular haemorrhage (IVH) grade III–IV [10], post-haemorrhagic hydrocephalus, hypotension defined by a mean arterial pressure less than 2 standard deviation (SD) for gestation, severe hypocapnia in mechanical ventilated neonates with a partial pressure of carbon dioxide less than 35 mm Hg, perinatal stress defined by pH < 7 and base excess ≤ -12 mmol/L, or haemoglobinopathies were excluded. Cranial ultrasound was performed in all neonates in order to rule out IVH III–IV, while haemoglobinopathy screening was performed only upon clinical suspicion.

Data collection

The perinatal and neonatal characteristics of the neonates were recorded including gestational age, gender, birth weight, body length and head circumference, mode of conception, full course of antepartum steroid administration, maternal preeclampsia or gestational diabetes, intrauterine growth velocity, normality of the antenatal Dopplers, mode of delivery, resuscitation required, APGAR score in the first and fifth minute, respiratory distress syndrome, duration of invasive and non-invasive mechanical ventilation, day of enteral feeding initiation, development of bronchopulmonary dysplasia, necrotising enterocolitis, sepsis, cranial ultrasound findings at discharge, and discharge body weight. Sepsis was defined by a positive blood culture; respiratory distress syndrome and bronchopulmonary dysplasia were defined according

to standard criteria; and necrotising enterocolitis according to modified Bell criteria [11]. Moreover, standard laboratory tests were performed on every study participant during the first, third and seventh day of life including haemoglobin (Hb), haematocrit (Hct), glucose and acid-base balance analysis. The vital signs were continuously recorded (Dräger Siemens SC 9000XL Monitor, Solna, Sweden) including heart rate, mean arterial pressure and pulse oxygen saturation (SpO₂). Mean blood pressure was recorded via an oscillometric technique with an inflatable cuff with 5-min intervals during NIRS measurements.

Transcranial Doppler measurements

We performed a colour transcranial Doppler, utilising the CX50 Philips ultrasound machine (Philips Medical Systems Nederland B.V., Best, The Netherlands), through the temporal window with the S8-3 probe on each neonate in the first 12 postnatal hours, and repeated on the third and seventh day of life. The middle cerebral artery haemodynamics were evaluated, according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology [12]. The mean velocity, peak systolic velocity and end diastolic flow were recorded, and the pulsatility index (PI) and resistance index (RI) were computed according to the formula: $PI = (\text{peak systolic velocity} - \text{end diastolic flow}) / \text{mean velocity}$ and $RI = (\text{peak systolic velocity} - \text{end diastolic flow}) / \text{peak systolic velocity}$, respectively.

Near-infrared spectroscopy monitoring

The NIRO-200NX Cerebral Oximeter Monitor (Hamamatsu Protonics® KK, Tokyo, Japan) was used to measure tissue oxygenation and perfusion. Two neonatal transducers containing a light-emitting diode and two sensors, the detection and the emission probe at a distance of 4 cm, were attached to each neonate. One was placed on the left and the other on the right frontoparietal forehead and held gently with a gauze bandage. The cerebral tissue oxygenation index (cTOI) and cerebral tissue haemoglobin index (cTHI) were computed using a spatially resolved spectroscopy algorithm. The cTOI is expressed as the percentage of oxygenated haemoglobin in real time and represents the mixed oxygenation of the cerebral compartments, as most (~75%) of the blood in the tissue is in the venous system [13]. The normal values of cTOI that have been proposed for healthy neonates depend on the different commercial devices and are estimated at 70–73% using NIRO-200NX. The cTHI, expressed in an arbitrary unit, provides a surrogate for total tissue Hb content within the cerebral tissue, and could be utilised as an indirect measure of blood flow and vasomotor activity. The cTHI represents the cumulative amount of oxygenated and non-oxygenated tissue Hb and is expressed in μmol . The cTHI reflects the cerebral perfusion and depends on the cardiac output and the cerebral vascular resistances.

Spectroscopic measurements were performed for 40 min each on the first, third and seventh postnatal day in all neonates. NIRS and SpO₂ signals were sampled at 2-s intervals and data were stored as numerical values in a personal computer. cTOI as well as cTHI were expressed as a median of 900 measurements, while cerebral fractional tissue oxygen extraction (cFTOE) was calculated from the formula $\text{SpO}_2\text{-TOI}/\text{SpO}_2$ [14].

Bayley-III Scale of Infant and Toddler Development

A neurodevelopmental assessment of SGA and AGA neonates that attended the follow-up appointment was performed at 24–36 months of age with the Bayley-III Scale of Infant and Toddler Development (BSID-III). The BSID-III includes the evaluation of five distinct areas of development: cognitive, communication (expressive and receptive language), motor (fine and gross), social/emotional and adaptive. Each scale is estimated with composite and subscale scores, in addition to normal centiles. The normal reference index that has been established for a composite score is 100 ± 15 , while for the subscale score it is 10 ± 3 . Values below 85 for composite and below 7 for subscale scores are considered as indicating neurodevelopmental impairment [15]. As BSID-III has not been standardized yet in the Greek population, a translated manual, questionnaire and evaluation form was adopted by the American edition, and the cognitive, communication and motor domains were evaluated.

Outcomes

The primary outcome was the evaluation of the cerebral oxygenation and perfusion in SGA and AGA neonates within the first, third and seventh postnatal day, with a subgroup analysis between SGA/IUGR and AGA neonates, and furthermore, the effect that perinatal parameters may have in cerebral oxygenation and perfusion.

The secondary outcome was the evaluation of any association between the cerebral oxygenation parameters or the clinical and laboratory characteristics and the neurodevelopmental outcome between the SGA and AGA neonates, assessed by the BSID-III index scores at 24–36 months of age.

Statistical analysis

The normality of the distributions of continuous variables was assessed by the Kolmogorov-Smirnov test. Continuous variables were expressed as mean $\pm$ SD or median [interquartile range (IQR)] as appropriate. Comparisons of continuous variables between SGA and AGA neonates, as well as between SGA/IUGR and AGA neonates, on the first, third and seventh postnatal day were performed using Student's unpaired *t*-test or the non-parametric Mann-Whitney test. Categorical variables were expressed as n (%) and compared with Pearson's chi-square (χ^2) test or Fisher's exact test. The effect of perinatal parameters on cerebral oxygenation and perfusion was assessed with Pearson's coefficient. Multivariate linear regression analysis was utilised for the adjustment of multiple confounders and the cerebral monitoring parameters associated with the BSID-III index scores at 24–36 months of age.

All performed tests were two-sided, and a P-value less than 0.05 was considered statistically significant (alpha 0.05). The data were analysed using SPSS Statistics Version 20.0 (IBM, Chicago, IL, USA). The power of the analysis was estimated using PASS 11.0 (NCSS, LLC, Kaysville, UT, USA), and sample sizes of 38 cases and 38 controls were estimated to achieve a 90% power to detect a difference of -10 on cTOI and 0.1 on cFTOE between the two groups with a significant level (alpha) of 0.05.

Results

During the study period, 48 SGA neonates (23 symmetrical and 27 asymmetrical) and accordingly 48 AGA controls were enrolled. The gestational age was similar between the two groups (32.8 ± 2.1 compared to 32.5 ± 1.9 , $P = 0.48$), while birth weight, body length and head circumference were significantly lower in the SGA neonates (Table 1). IUGR was diagnosed in 29 (60%) of the SGA neonates. Males were predominant in AGA compared to the SGA group (65% compared to 42%, $P = 0.04$). There were no significant differences regarding the neonatal characteristics such as respiratory distress syndrome, length of invasive or non-invasive mechanical ventilation, sepsis, necrotising enterocolitis or development of bronchopulmonary dysplasia between the SGA and AGA neonates. Also, no significant differences were noted in the cranial ultrasound findings at discharge between the two groups. Enteral feeding was initiated in 2.2 ± 1.0 days in SGA neonates compared to 1.7 ± 0.6 days in AGA neonates ($P = 0.008$). Finally, the SGA neonates had significantly higher levels of Hb and Hct on the first and third postnatal day compared to AGA neonates, but otherwise no differences were noted on the other laboratory findings (Table 2).

Cerebral oxygenation and perfusion and Doppler parameters

Cerebral oxygenation was expressed by the averaged value of cTOI and cFTOE and was equal between SGA and AGA neonates during the first, third and seventh postnatal day (Table 2). In subgroup analysis, male SGA neonates had higher cTOI on the first postnatal day compared to female SGA neonates ($73 \pm 7\%$ vs. $69 \pm 7\%$, $P = 0.04$). Of note, cerebral perfusion that was expressed by the average cTHI was significantly higher in SGA neonates on the first postnatal day, but this difference was diminished on the subsequent measurements on the third and seventh postnatal days.

With regard to the colour Doppler parameters, no significant differences were recorded in the PI or RI between the two groups of neonates. The longitudinal analysis of cTOI, cTHI, PI and RI within the first seven postnatal days in SGA and AGA neonates is presented in Figure 1. A subgroup analysis was also performed between the SGA/IUGR and the AGA neonates with respect to cerebral oxygenation and perfusion and Doppler parameters, which also revealed a significant higher cTHI in the SGA/IUGR neonates during the first postnatal day (Supplementary Table 1).

Table 1: Perinatal and neonatal characteristics of SGA and AGA neonates.

Characteristics	SGA (n = 48)	AGA (n = 48)	P-value
Gestational age, weeks	32.8 ± 2.1	32.5 ± 1.9	0.48
Birth weight, g	1406 ± 402	1969 ± 526	<0.001
Body length, cm	40.6 ± 3.9	43.8 ± 3.6	<0.001
Head circumference, cm	28.5 ± 2.4	30.9 ± 2.4	<0.001
Gender, male	20 (42)	31 (65)	0.04
Conception, <i>in vitro</i> fertilisation	14 (31)	15 (35)	0.82
Antenatal steroid administration	41 (87)	44 (92)	0.52
Preeclampsia	15 (31)	6 (13)	0.04
Gestational diabetes	9 (19)	6 (13)	0.57
Singleton pregnancy	48 (100)	48 (100)	1.00
Intrauterine growth restriction	29 (60)	–	<0.001
Delivery mode, caesarean section	48 (100)	46 (96)	0.49
Resuscitation at delivery room	2 (4)	2 (4)	1.00
Apgar first minute	8 (7–8)	8 (7–8)	0.44
Apgar fifth minute	9 (8–9)	9 (8–9)	0.66
Respiratory distress syndrome	16 (36)	21 (47)	0.39
Invasive mechanical ventilation, days	0 (0–4)	0 (0–1)	0.43
Non-invasive mechanical ventilation, days	2 (0–3)	1 (0–4)	0.65
Bronchopulmonary dysplasia	4 (8)	4 (8)	1.00
Necrotising enterocolitis	–	1	1.00
Late-onset sepsis	9 (21)	4 (9)	0.22
Initiation of enteral feeding, days	2.2 ± 1.0	1.7 ± 0.6	0.008
Cranial ultrasound at discharge			
Normal	44 (92)	45 (94)	1.00
Echogenicity	4 (8)	3 (6)	
Discharge weight, g	1948 ± 200	2275 ± 311	<0.001

AGA, appropriate for gestational age; SGA, small for gestational age. Continuous variables are expressed as mean ± SD or median (IQR). P-values of Student's *t*-test or the Mann-Whitney *U* test. Categorical variables are expressed as n (%). P-values of chi-square test or Fisher's exact test.

Table 2: Cerebral oxygenation and perfusion data, Doppler and laboratory findings of SGA and AGA neonates.

	Day 1		P-value	Day 3		P-value	Day 7		P-value
	SGA	AGA		SGA	AGA		SGA	AGA	
Mean cTOI, %	71 ± 7	72 ± 8	0.50	73 ± 6	71 ± 8	0.20	70 ± 6	70 ± 6	0.77
Mean cFTOE	0.26 ± 0.08	0.25 ± 0.08	0.59	0.25 ± 0.07	0.27 ± 0.08	0.23	0.28 ± 0.06	0.28 ± 0.06	0.90
Mean cTHI	1.4 ± 0.6	1.1 ± 0.5	0.04	1.3 ± 0.3	1.1 ± 0.4	0.07	1.1 ± 0.3	1.1 ± 0.4	0.66
Mean pulsatile index	1.41 ± 0.36	1.42 ± 0.31	0.94	1.34 ± 0.28	1.38 ± 0.28	0.52	1.5 ± 0.24	1.43 ± 0.26	0.13
Mean resistance index	0.71 ± 0.08	0.73 ± 0.08	0.34	0.71 ± 0.06	0.71 ± 0.07	0.71	0.72 ± 0.03	0.73 ± 0.06	0.90
SatO ₂	96.9 ± 2.7	97.1 ± 2.5	0.75	97.6 ± 2.4	97.6 ± 2.3	1.00	98.4 ± 1.9	98.3 ± 1.8	0.67
Mean arterial pressure, mm Hg	45.9 ± 8.2	47 ± 10.4	0.64	53.3 ± 8.9	55.4 ± 13.9	0.50	54.5 ± 10.4	57.4 ± 11.6	0.56
Heart rate, b/m	139 ± 15	143 ± 11	0.08	136 ± 15	142 ± 14	0.06	140 ± 13	142 ± 11	0.31
Hb, mg/dL	17.5 ± 1.9	15.8 ± 1.5	<0.001	16.3 ± 2.3	15.2 ± 1.5	0.01	14.9 ± 1.7	14.5 ± 1.3	0.41
Hct, %	51.9 ± 5.9	46.8 ± 4.5	<0.001	48.2 ± 6.5	44.7 ± 4.5	0.007	43.8 ± 5	42.7 ± 4.1	0.30
Glucose, mg/dL	75 ± 35.1	71 ± 26.7	0.63	81.1 ± 27.5	76.5 ± 19.1	0.38	85.3 ± 27	83.3 ± 19.9	0.70
pH	7.42 ± 0.07	7.41 ± 0.07	0.28	7.44 ± 0.07	7.43 ± 0.06	0.34	7.45 ± 0.06	7.43 ± 0.07	0.11
pCO ₂ , mm Hg	34.5 ± 8.2	35.3 ± 7.7	0.66	30.5 ± 7.5	32.9 ± 6.6	0.11	31.8 ± 5.5	33.0 ± 8.2	0.22
Base excess, mmol/L	−1.4 ± 2.0	−2.2 ± 2.3	0.07	−2.0 ± 3.3	−1.9 ± 1.7	0.77	−0.9 ± 2.7	−1.8 ± 2.3	0.13

AGA, appropriate for gestational age; cFTOE, cerebral fractional oxygen extraction; cTHI, cerebral tissue haemoglobin index; cTOI, cerebral tissue oxygenation index; SGA, small for gestational age; SpO₂, oxygen saturation. Continuous variables are expressed as mean ± SD. P-values of Student's *t*-test.

Figure 1: Longitudinal values of cTOI, cTHI, PI and RI within the first 7 days of life in SGA and AGA neonates. cTOI, Cerebral tissue oxygenation index; cFTOE, cerebral fractional oxygen extraction; cTHI, cerebral tissue haemoglobin index; PI, pulsatile index; RI, resistance index; SGA, small for gestational age; AGA, appropriate for gestational age.

Table 3: Effect of postnatal age, size at birth, gender and covariates on cTOI, cFTOE and cTHI at birth.

Variables	cTOI		cFTOE		cTHI	
	r	P-value	r	P-value	r	P-value
Gestational age	0.168	0.10	0.054	0.60	0.030	0.78
Size at birth	0.070	0.50	0.071	0.49	0.141	0.20
Intrauterine growth restriction	0.022	0.83	0.064	0.54	0.037	0.74
Gender	0.210	0.04	0.119	0.05	0.035	0.75
Mean pulsatile index	0.054	0.61	0.056	0.59	0.004	0.97
Mean resistance index	0.048	0.65	0.046	0.66	0.084	0.45
SatO ₂	0.150	0.07	0.073	0.48	0.047	0.67
Mean arterial pressure, mm Hg	0.143	0.23	0.130	0.28	0.077	0.55
Hb, mg/dL	0.009	0.93	0.004	0.97	0.169	0.13

cFTOE, cerebral fractional oxygen extraction; cTHI, cerebral tissue haemoglobin index; cTOI, cerebral tissue oxygenation index; SpO₂, oxygen saturation.

The effect of gestational age, size at birth, IUGR, gender and other examined parameters on cTOI, cFTOE and cTHI is presented in Table 3. Male gender had a significant effect ($r = 0.210$, $P = 0.04$) on the cTOI at birth.

BSID-III index scores

Overall, 46 (48%) neonates attended the follow-up and had a neurodevelopmental assessment at 24–36 months of age (Table 4). Twenty-three SGA infants were evaluated at a mean corrected age of 27.8 ± 2.9 months and 23 AGA infants at a mean corrected age of 27.4 ± 1.8 months. There were no significant differences between the SGA and AGA infants regarding the composite index scores in the cognitive (94 ± 8 compared to 95 ± 16 , $P = 0.86$), communication (103 ± 17 compared to 94 ± 20 , $P = 0.13$) and motor domains (109 ± 13 compared to 104 ± 18 , $P = 0.24$), respectively. None of the participants had developed cerebral palsy. Accordingly, the same findings were demonstrated when a subgroup analysis between SGA/IUGR and AGA neonates was performed (Supplementary Table 2).

Regression analysis adjusting for any other confounding factors revealed that cTOI and cTHI during the first week of life were not significantly associated with the composite index scores. Of note, the length of the mechanical ventilation and the event of late-onset sepsis were significant risk factors affecting the cognitive and the communication composite index scores of the BSID-III assessment, respectively (Table 5).

Discussion

The findings of the current study suggested that neonates born SGA showed, compared to AGA, similar values of cerebral oxygenation during the first postnatal week. Of note, males born SGA had increased cerebral oxygenation at birth compared to SGA females. A transient increase in cerebral perfusion was only recorded in SGA neonates during the first postnatal day, which gradually diminished within the first postnatal week.

Previous studies have suggested that preterm neonates who were born SGA had higher cerebral oxygenation during the first postnatal days [6, 8, 16]. More likely, this higher cerebral oxygenation was related to a prenatal redistribution of the blood flow, mainly in cases of IUGR, as an attempt of the fetus to preserve the cerebral oxygen supply. In particular, male SGA neonates were found to have significantly higher values of oxygenation and although evidence suggests that female neonates could have enhanced oxygen consumption in the context of higher metabolic rates, most probably this reflects physiologic differences rather than a pathologic phenomenon [8]. Our findings could not detect any difference in cerebral oxygenation between SGA and AGA neonates and most importantly, the values of cerebral oxygenation that were found in our study were within normal limits.

Interestingly, although cerebral perfusion and oxygenation are tightly linked, our findings could only suggest that cerebral perfusion was transiently higher in SGA neonates during the first postnatal day. The cTOI is influenced by the oxygen delivery, the tissue oxygen consumption

Table 4: Characteristics of BSID-III index scores at 24–36 months of age between SGA and AGA neonates.

Characteristics	SGA (23)	AGA (23)	P-value
Gestational age, weeks	32.7 ± 1.9	31.9 ± 1.7	0.15
Chronological age, months	27.8 ± 2.9	27.4 ± 1.8	0.52
Cognitive scaled score	9 ± 2	9 ± 3	0.86
Cognitive composite score	94 ± 8	95 ± 16	0.86
Suboptimal cognitive composite score (<85)	2 (9)	5 (22)	0.41
Expressive language scaled score	10 ± 4	8 ± 4	0.19
Receptive language scaled score	11 ± 3	10 ± 3	0.14
Communication composite score	103 ± 17	94 ± 20	0.13
Suboptimal communication score (<85)	2 (9)	7 (30)	0.14
Fine motor scaled score	11 ± 2	11 ± 3	0.61
Gross motor scaled score	12 ± 3	10 ± 4	0.15
Motor composite score	109 ± 13	104 ± 18	0.24
Suboptimal motor composite score (<85)	–	1 (5)	1.00

AGA, appropriate for gestational age; BSID-III, Bayley-III Scales for Infant and Toddler Development; SGA, small for gestational age. Continuous variables are expressed as mean $\pm$ SD. P-values of Student's *t*-test. Categorical variables are expressed as n (%). P-values of Fisher's exact test.

Table 5: Linear regression analysis of the effect of risk factors on the cognitive, communication and motor composite index scores.

Variables	Beta	Standard error	P-value	95% CI
Cognitive composite index score				
Birth weight	0.003	0.009	0.76	0.015–1.020
Gender, male	5.462	5.274	0.31	0.810–16.303
Size at birth	0.316	5.440	0.95	0.086–11.497
Mean cTOI	0.028	0.339	0.93	0.008–1.724
Mean cTHI	2.212	3.170	0.49	0.727–4.303
Late-onset sepsis	5.656	3.753	0.14	–2.059–13.370
Length of mechanical ventilation	4.732	2.583	0.04	3.041–6.577
Bronchopulmonary dysplasia	7.481	6.964	0.29	0.834–21.795
Communication composite index score				
Birth weight	0.002	0.013	0.87	0.001–1.025
Gender, male	13.953	8.236	0.10	0.175–31.080
Size at birth	7.330	8.049	0.37	0.408–24.068
Mean cTOI	1.000	0.506	0.06	0.052–2.053
Mean cTHI	0.959	5.857	0.87	0.222–13.140
Late-onset sepsis	14.706	6.031	0.02	2.164–27.248
Length of mechanical ventilation	9.133	4.372	0.04	1.040–18.226
Bronchopulmonary dysplasia	3.232	10.573	0.76	0.754–25.219
Motor composite index score				
Birth weight	0.010	0.261	0.32	0.003–1.011
Gender, male	11.592	6.538	0.08	0.901–25.085
Size at birth	2.150	6.371	0.73	0.099–15.299
Mean cTOI	0.724	0.395	0.07	0.091–1.539
Mean cTHI	1.924	3.896	0.62	0.065–6.118
Late-onset sepsis	6.413	4.774	0.19	0.344–16.266
Length of mechanical ventilation	8.116	3.321	0.02	1.262–14.970
Bronchopulmonary dysplasia	0.795	8.422	0.92	0.178–16.588

cTHI, cerebral tissue haemoglobin index; cTOI, cerebral tissue oxygenation index.

and the tissue oxygen extraction, while on the other hand, cTHI reflects the cerebral perfusion and depends on the cardiac output and cerebral vascular resistances. In cases where the metabolic rate and thus the oxygen consumption is increased, the cerebral perfusion might increase in order to maintain adequate oxygen delivery and optimal cerebral oxygenation. The higher metabolic rate of SGA infants during the early period of adaptation might explain these findings, as a higher perfusion might be required for maintaining an optimal cerebral tissue oxygenation. Previous studies have shown that fetuses exposed to IUGR are susceptible to prolonged periods of hypoxia and diminished blood supply *in utero*. In an attempt to maintain optimal oxygen supply to the brain, growth-restricted fetuses increase their cerebral perfusion and Hb, leading to compensated polycythemia [6, 7, 17]. This typical hemodynamic adaptation, called the brain-sparing effect, represents an attempt to preserve oxygen and nutrient supply to the brain of IUGR fetuses. With advancing postnatal age, these changes in cerebral perfusion and oxygenation become less apparent. Evidence

from previous studies have shown that the brain-sparing effect may be sustained for up to 4 postnatal days [8, 18]. In accordance with previous findings, our data suggested that the differences found in cerebral perfusion between SGA and AGA neonates gradually diminished after the third postnatal day.

The clinical significance of cerebral oxygenation and perfusion with respect to neurodevelopmental outcomes was also examined in our study. Neonates born IUGR are at potential risk of an adverse long-term neurodevelopmental outcome [1, 2], which, however, is influenced by multiple perinatal factors such as low birth weight, hemodynamically significant patent ductus arteriosus, sepsis, prolonged mechanical ventilation or nutrient deprivation [19–21]. In our cohort, we found no differences between SGA and AGA neonates in the BSID-III index scores, and in the cognitive, communication and motor domains. When adjusting for confounding factors, we found that the length of mechanical ventilation and late-onset sepsis were significantly related to lower index cognitive and communication scores at 24–36 months of age, irrespective of the size at birth.

Prolonged respiratory support, long periods of hypoxia and exposure to oxidative stress have been associated with spatial and memory deficits and an increased risk for neurodevelopmental impairment [22–24]. Moreover, neonatal sepsis and systemic inflammatory response syndrome have been related to poor neurodevelopmental outcome and cerebral injury [25–27]. Our findings, in accordance with previous studies, indicate the impact of serious morbidities on the vulnerable neonatal brain.

There are several limitations to the current study that need to be addressed. First, we were unable to directly measure the cardiac output and thus the cerebral blood flow in our cohort. Although the NIRS measurement of cTHI is useful in the clinical setting, it needs further validation as it may only partially explain the hemodynamic changes of SGA and AGA neonates during the first postnatal week. Nonetheless, the changes in cerebral oxygenation and perfusion between SGA and AGA neonates may reflect a physiological adaptation rather than an underlying pathology. Although we evaluated the middle cerebral artery haemodynamics, we could not evaluate the velocity waveform of the carotids that might have provided a better indication of changes in cerebral perfusion. Furthermore, the cohort of our study consists of relatively mature infants, and although our findings reflect the cerebral hemodynamic changes in very preterm and late preterm infants, they might not be precisely applicable in compromised extremely preterm infants. Finally, the clinical significance and the impact on long-term neurodevelopmental outcome may be influenced by multiple factors. In our study, prolonged mechanical ventilation and sepsis were associated with lower BSID-III index scores at 24–36 months of age. However, neurological development is a continuous dynamic procedure, and apart from clinical morbidities is also affected by environmental factors, such as family influence and socioeconomic factors.

The current study suggested that the cerebral oxygenation was equal between SGA and AGA neonates, while cerebral perfusion was transiently increased in SGA neonates during the first postnatal day. The neurodevelopmental outcome was not affected by cerebral oxygenation and perfusion during the first postnatal week; however, it was significantly associated with neonatal morbidities such as prolonged mechanical ventilation and sepsis. Further studies are warranted to examine the clinical effects of the changes to cerebral oxygenation and perfusion beyond the first week of age.

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