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Cerebral Blood Flow Measured by Phase-Contrast Magnetic Resonance Angiography in Preterm and Term Neonates

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Keywords
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Abstract
Background: Preterm infants show a decreased tortuosity in all proximal segments of the cerebral vasculature at term-equivalent age (TEA). Recently MRI techniques were developed to measure cerebral blood flow (CBF) based on phase-contrast images. ***Objectives:*** We hypothesized that arterial CBF corrected for brain size differs between full-term and preterm infants at TEA. ***Methods:*** 344 infants without major brain abnormalities had a cranial MRI for clinical reasons including phase-contrast magnetic resonance angiography (PC-MRA) around TEA (mean 41.1 ± SD 1.2 weeks). This cohort consisted of 172 preterm infants (gestational age at birth 24.1–31.9 weeks) and 172 term-born infants (gestational age at birth 37.0–42.6 weeks). The total CBF in milliliters/minute was calculated by adding the blood flow of the carotid and basilar arteries, and compared to age at scan, body weight, and several parameters of estimated brain size. ***Results:*** After logarithmic transformation, total CBF was associated with body weight, estimated brain weight, head circumference, and 2D brain surface measurements at TEA. Total CBF was significantly (9–12%) higher in term compared to preterm infants after correction for 2D brain surface measurements, head circumference or postmenstrual age at MRI ($p < 0.05$). ***Conclusions:*** Total CBF as measured by PC-MRA was associated with body and (estimated) brain weight and 2D brain surface measurements and was higher in term compared to preterm born infants.

Introduction

A sufficient and stable blood flow to the brain is essential for brain function and development. Alterations or disruptions in cerebral blood flow (CBF) play an important role in the pathogenesis of neonatal brain injury, such as ischemia or hemorrhage [1, 2]. Several studies have demonstrated that flow in the cerebral arteries increases along with postmenstrual age and weight [3, 4]. Additionally, others have found decreased tortuosity in all proximal segments of the cerebral arteries in preterm

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Table 1. Clinical characteristics of participants

	Total group (n = 344)	Preterm infants (n = 172)	Term infants (n = 172)	p value
GA, weeks	33.6±6.5	27.3±1.7	39.8±1.4	<0.0001
Birth weight, g	2,219±1327	989±310	3,463±597	<0.0001
Male	189 (55)	94 (55)	95 (55)	ns
Reason for scanning				
Standard clinical care	174 (51)	130 (76)	44 (26)	
Perinatal asphyxia	68 (20)	1 (1)	67 (39)	
Seizures	34 (10)	1 (1)	33 (19)	
Ultrasound abnormalities	28 (8)	18 (11)	10 (6)	
Study protocol	16 (5)	16 (9)	0 (0)	
Other	24 (7)	6 (4)	18 (11)	
Postmenstrual age at time of scan, weeks	41.1±1.2	41.2±0.7	41.0±1.5	ns
Weight at time of scan, g	3,523±568	3,455±528	3,578±593	ns
Head circumference at time of scan, cm	35.1±1.6	35.2±1.6	34.9±1.7	ns
Brain injury on MRI				
None	233 (68)	103 (60)	130 (76)	
IVH ≤grade 2	64 (19)	58 (34)	6 (4)	
Mild white matter injury	15 (4)	2 (1)	13 (8)	
Minor stroke	16 (5)	4 (2)	12 (7)	
PHVD without intervention	5 (2)	4 (2)	1 (1)	
Other[a]	11 (3)	1 (1)	10 (6)	
2D brain surface measurements, mm^2	7,406±634	7,370±653	7,442±615	ns
Total brain volume, excluding extracerebral CSF, mL	353±34	353±34	–	–

Data reported as mean ± SD or number (percentage), where applicable. p values are given for differences between preterm and term infants (2-tailed significance). CSF, cerebrospinal fluid; GA, gestational age; MRI, magnetic resonance imaging; IVH, intraventricular hemorrhage; PHVD, posthemorrhagic ventricular dilatation.
[a] Other diagnoses included, i.e., intraparenchymal hemorrhage <2 cm, viral meningitis.

infants imaged at term-equivalent age (TEA) compared to term-born infants, which was found to persist until 18 months of age [5]. These studies indicate that preterm birth may alter the development of cerebral blood vessels, making them more vulnerable to neonatal brain injury.

In the past decades, different techniques have been developed to measure CBF. The first measurements of blood flow were performed by Schmidt and Kety [6] in 1940 by administering nitrous oxide [7]. Since then, different techniques for measurements of CBF were developed. These include positron emission tomography, xenon-enhanced computed tomography, and venous occlusion plethysmography [4, 8]. More recently, techniques have been developed that can measure CBF noninvasively, including Doppler-derived measurements of blood flow velocity [9]. However, volume flow measurements using Doppler may be difficult due to the small diameter of the feeding intracranial arteries in infants resulting in imprecise measurements [10]. Phase-contrast magnetic resonance angiography (PC-MRA) appears to be a useful technique to reliably measure CBF noninvasively. These measurements at the base of the skull are fast to perform with a scan time of less than a minute providing the volume flow in milliliters/minute [4, 9, 11]. Formerly, reference values for PC-MRA determined CBF in children have only been presented in smaller cohorts [12, 13].

This study aims to provide reference values for PC-MRA-determined CBF in a large cohort of preterm and term infants. In order to adequately correct CBF for measures of brain size, associations between CBF and age, weight, and various estimates of brain size at the time of the scan are investigated. Furthermore, differences in CBF between preterm- and term-born infants are investigated.

Methods

A total of 528 infants had an MRI scan performed at TEA during or after admission to the Neonatal Intensive Care Unit of the Wilhelmina Children's Hospital, University Medical Center

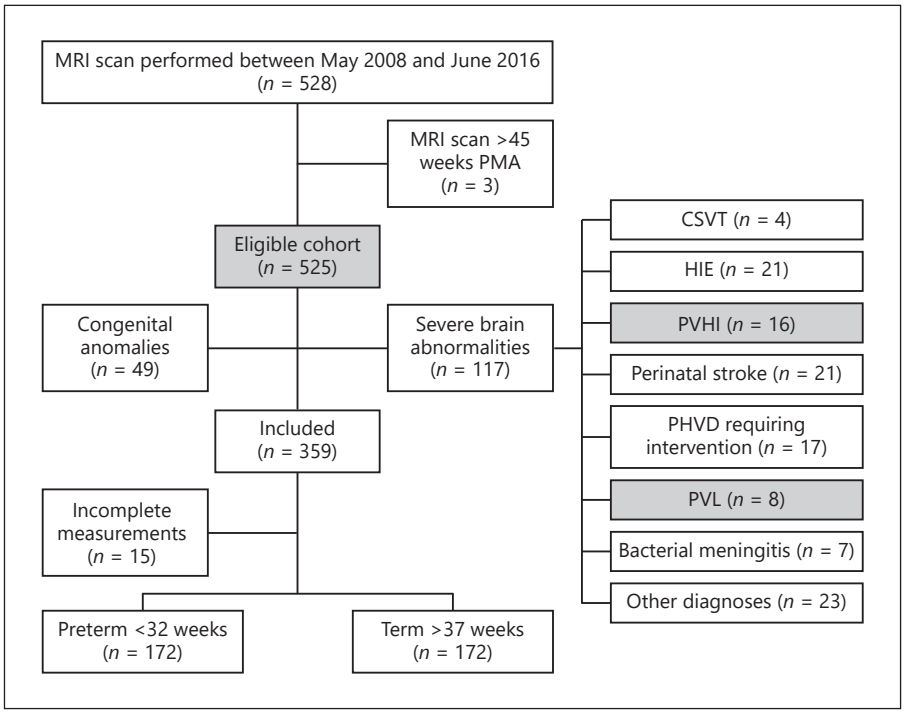

Fig. 1. Flowchart of inclusion of the study cohort. PMA, postmenstrual age; CSVT, cerebral sinovenous thrombosis; HIE, hypoxic ischemic encephalopathy; PVHI, periventricular hemorrhagic infarction; PHVD, posthemorrhagic ventricular dilatation; PVL, periventricular leukomalacia.

Utrecht, Utrecht, the Netherlands, between May 2008 and June 2016. Clinical details of the preterm infants (gestational age <32 weeks) and term-born infants are presented in Table 1. Infants were scanned as part of standard clinical care protocols [14, 15], or because of perinatal asphyxia, presence of seizures or ultrasound abnormalities on routine examinations during Neonatal Intensive Care Unit admission. Sixteen preterm infants were included in a prospective study and therefore had an MRI at TEA [16, 17]. A flowchart of the included patients is presented in Figure 1. Infants with major MRI abnormalities (n = 117) were excluded from the present study (Fig. 1).

Magnetic Resonance Imaging

All MRI scans were performed on a 3.0-T whole-body Achieva system (Philips Medical Systems, Best, the Netherlands) using an 8-channel receiver sense head coil. During the imaging procedure, infants were sedated to prevent motion artifacts. Sedation consisted of using oral chloral hydrate 50–60 mg/kg in both preterms at TEA and term infants or a combination of pethidine, chlorpromazine, and promethazine intramuscularly in term infants only as described previously [18]. The imaging protocol including the use of sedation has been described previously [14, 19]. During the MRI, infants were monitored using transcutaneous pulse oximetry (Nonin Medical Incorporated, Minneapolis, MN, USA), and hearing protection was used in all infants using Minimuffs (Natus Medical Incorporated, San Carlos, CA, USA) and Earmuffs (EM's 4 Kids, Brisbane, Australia). To prevent excessive head movement and for additional hearing protection, a vacuum pillow (Med-Tec, Orange City, IA, USA) was used. A neonatologist or physician assistant was present throughout the examination.

CBF Measurements

As part of the standard clinical MRI protocol, phase-contrast (PC) images were made as described previously [9]. First a 2D PC sagittal survey image was made (Fig. 2; slice thickness 40 mm; field of view 200 × 200 mm; matrix 204 × 102; number of averages 1; velocity sensitivity 15 cm/s; flip angle 15°; scan time 16 s). Then, a 2D PC section was positioned perpendicular to the basilar artery just below the carotid siphon (shortest TR 13–16 ms; shortest TE 8–10 ms; slice thickness 5 mm; field of view 150 mm anterior-posterior [AP] × 103 mm left-right [LR]; matrix 128 × 88; number of averages 4; velocity sensitivity 30 cm/s; flip angle 10°; scan time 20 s). In case of aliasing, the velocity sensitivity was increased to 60 cm/s.

With Philips software on the 3.0-T MR system, quantitative flow values (mL/min) were calculated in each vessel by integrating across manually drawn regions of interests that enclosed the vessel lumen on the amplitude images closely as reported previously [9, 20]. Background correction was performed by the Philips software. The total CBF was calculated by adding the flow (in mL/min) of both carotid arteries and the basilar artery (Fig. 2). CBF is a mean volume flow in milliliters/minute during the cardiac cycle, as it does not synchronize with cardiac output.

Brain Size Measurements

In order to adequately control CBF for brain dimensions, surrogate parameters that approximate brain size are investigated. These include postmenstrual age, head circumference, weight, 2D brain surface measurements, 3D total brain volume (TBV) and estimated brain weight. Brain weight was estimated using the formula log10(brain weight) = 0.64 log10(birth weight) + 0.35 as described by Jordaan [21] in 1976, where birth weight was replaced by weight at the time of the MRI.

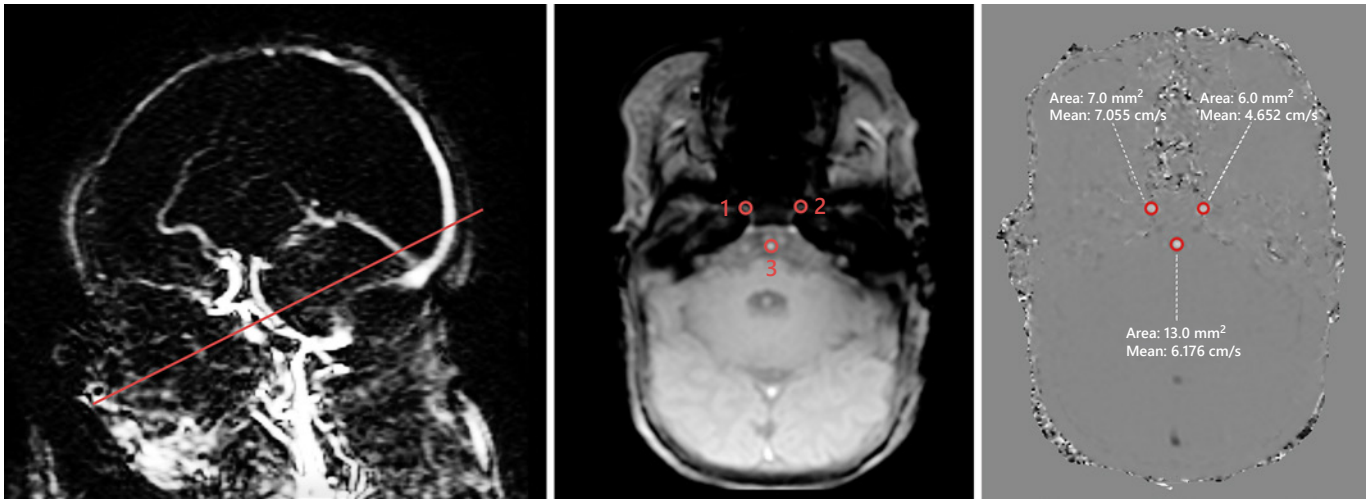

Fig. 2. Example of phase-contrast (PC) magnetic resonance angiography. Position of the 2D PC section perpendicular to the basilar artery (BA), just below the carotid siphon to measure the flow in the internal carotid arteries (ICAs): (1) right-sided ICA; (2) left-sided ICA; (3) BA. The total CBF was calculated by adding the flow (in mL/min) of both ICAs and the BA (1–3).

For all infants, 2D brain surface measurements were performed as described previously [22]. The AP measurements were preferentially carried out in the sagittal plane, with the measurement tool as close to the longitudinal fissure as possible. The LR measurements were obtained in either the axial or coronal plane. Using the AP maximum length and LR maximum width, a 2D oval-shaped slice was calculated using the formula: 2D slice = $\pi \times 0.5$ AP (mm) $\times 0.5$ LR (mm) [22].

In a subset of 89 preterm infants, semiautomatic segmentation of the different brain structures was performed. Segmentations were automatically obtained with in-house-developed image processing software, after which segmentations were manually edited to increase accuracy [23]. With this method, volumetric measurements of the brain stem, cerebellum, basal ganglia and thalamus, myelinated white matter, unmyelinated white matter, cortical gray matter, ventricular cerebrospinal fluid, and extracerebral cerebrospinal fluid were obtained. To calculate TBV, all these brain structures except for extracerebral cerebrospinal fluid were summed.

Statistical Analysis

A Shapiro-Wilk test was used to determine normality of the data distribution. In case of normal data distribution, patient characteristics were expressed as means ± SD. Otherwise, median and interquartile ranges were given. Associations between PC-MRA determined CBF and either head circumference, weight, 2D brain surface measurements, or TBV were determined using simple linear regression analysis. Differences in CBF between preterm- and term-born infants were tested using the Mann-Whitney U test, since these data were nonnormally distributed. In multivariable analyses, CBF was log-transformed to normalize the data. Linear regression was used to identify independent factors that were associated with log-CBF. p values <0.05 were considered significant. Statistical analysis was performed with SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

This cohort consisted of 344 infants scanned at a mean postmenstrual age of 41.1 ± 1.2 weeks. There were no significant differences in measures of brain size, between preterm infants and term infants (Table 1). Mild to moderate brain injury was present in 111 infants (32%) and included intraventricular hemorrhage (IVH) ≤grade 2, mild white matter injury, minor strokes, and posthemorrhagic ventricular dilatation without intervention (Table 1). 2D brain surface measurements strongly associated with TBV in preterm infants as illustrated in the online supplementary Figure (for all online suppl. material, see www.karger.com/doi/10.1159000494368).

Cerebral Blood Blow

CBF ranged between 30 and 332 mL/min (median 98.4; interquartile ranges 76.4–127.7 mL/min). Median CBF was significantly higher in term infants (106.2 mL/min) compared to preterm infants (90.9 mL/min; $p < 0.01$). CBF corrected for body weight ranged between 9.8 and 94.0 mL/min/kg (median 28.5 mL/min/kg). CBF corrected for estimated brain weight ranged be-

Table 2. Linear regression model associating independent factors with LnCBF were tested in a multivariable modeling

Dependent variable	Factors	Coefficient	95% CI
LnCBF, mL/min	term born	0.11	0.03–0.19
	postmenstrual age at MRI (weeks)	0.06	0.03–0.10
LnCBF, mL/min	term born	0.08	0.00–0.16
	body weight at MRI (kg)	0.10	0.03–0.17
LnCBF, mL/min	term born	0.09	0.00–0.18
	head circumference at MRI (cm)	0.04	0.01–0.06
LnCB, mL/min	term born	0.08	0.00–0.16
	estimated brain weight at MRI (100 g)	0.14	0.05–0.23
LnCBF, mL/min	term born	0.09	0.01–0.17
	2D brain surface measurements ($cm^{2)}$	0.010	0.004–0.017

Being term born increased the LnCBF when correcting for several parameters of brain size.

tween 8.1 and 79.5 mL/100 g/min (median 23.6 mL/100 g/min). CBF corrected for body weight or brain weight did not differ significantly between term and preterm infants.

Brain Size Correlates with CBF

There were significant positive associations between PC-MRA-determined CBF and either postmenstrual age at the time of the scan in weeks (coefficient 5.50; 95% CI 1.76–9.24), weight at the time of the scan in kilograms (coefficient 12.6; 95% CI 4.9–20.2), head circumference at the time of the scan in centimeters (coefficient 3.33; 95% CI 0.39–6.26), estimated brain weight in grams (coefficient 0.17; 95% CI 0.07–0.27), or 2D brain surface measurements in square centimeters (coefficient 0.010; 95% CI 0.003–0.017). There was no significant association between CBF and TBV.

Since CBF data were not normally distributed, log-transformation was applied for further analyses, which normalized the CBF data. LnCBF was still significantly associated with postmenstrual age at the time of the scan in weeks (coefficient 0.06; 95% CI 0.03–0.10), body weight at the time of the scan in kilograms (B = 0.10; 95% CI 0.03–0.17), head circumference at the time of the scan (coefficient 0.034; 95% CI 0.007–0.060), estimated brain weight in 100 g (coefficient 0.14; 95% CI 0.05–0.23), and 2D brain surface measurements in square centimeters (coefficient 0.010; 95% CI 0.004–0.017). Other parameters such as gender and MRI abnormalities were not significantly associated with (Ln) CBF.

Multivariable Modeling

Using linear regression, independent factors that were associated with LnCBF were tested in a multivariable model. Full-term infants had higher LnCBF values than preterm infants after correction for postmenstrual age at the time of the scan. In addition, LnCBF was dependent on head circumference, estimated brain weight or 2D brain surface measurements (Table 2; Fig. 3).

Discussion

This study aims to provide reference values for PC-MRA-determined CBF in a large cohort of preterm and term infants. PC-MRA-measured CBF ranged from 30 to 332 mL/min with a median of 98 mL/min, which is in line with our previous studies [4, 9]. This relatively large variation of CBF between neonatal subjects has been described previously [7]. Additionally, median CBF per kilogram body weight was comparable to our previous study (29 mL/min/kg vs. 25 mL/min/kg), although our slightly higher variables could be explained by the fact that infants in our study did not have major brain abnormalities [4]. Capel et al. [13] described a higher mean arterial CBF of 180 mL/min, but their cohort consisted mainly of older children (n = 23 between 5 days and 68 months).

CBF corrected for estimated brain weight ranged between 8.1 and 79.5 mL/100 g/min with a median of 23.6, mean 25.6 ± 9.9 ml/100 g/min. Vutskits [7] summarized CBF values per 100 g brain tissue in infants as measured

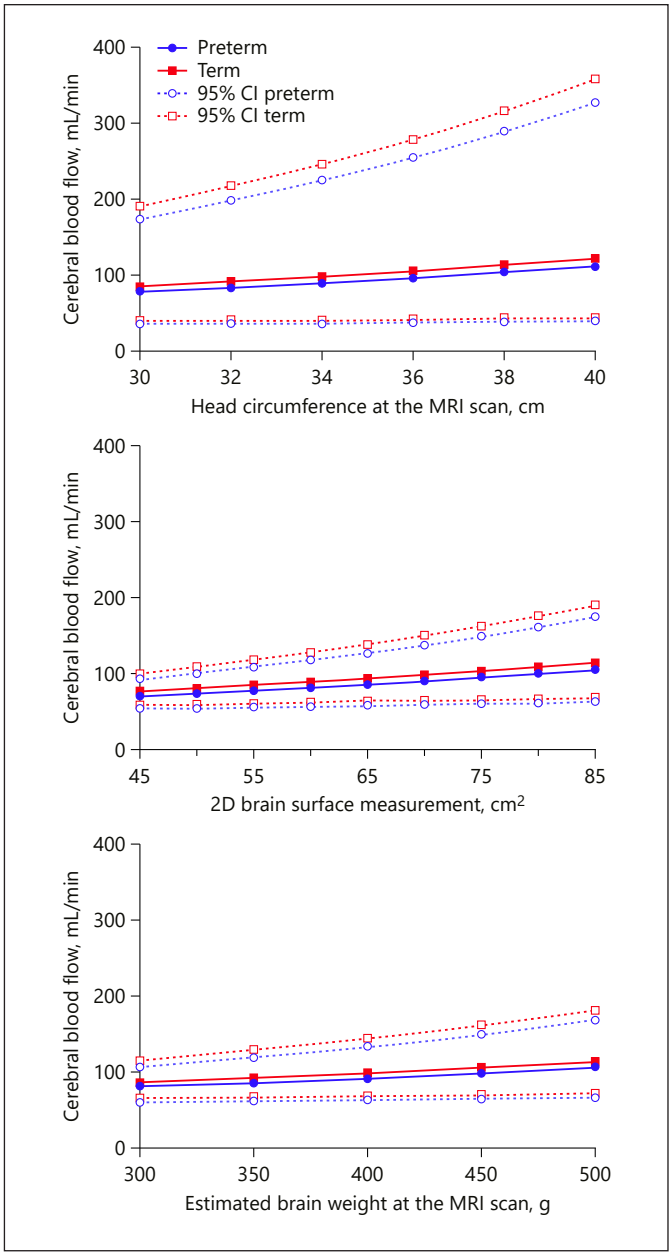

Fig. 3. Reference lines for total cerebral blood flow (in mL/min) for term (blue) and preterm (red) infants per estimate of brain size (head circumference on MRI in centimeters; 2D volume on MRI in square centimeters; estimated brain weight on MRI in grams).

by ^{133}Xenon clearance, position emission tomography and near-infrared spectroscopy in their review. Most studies were performed within a few days after birth and measured ranges of CBF between 4.3 and 19.9 mL/100 g/min [24] varying between 33 and 55 mL/100 g/min, comparable to our data [25]. A study from our group measuring CBF by pulsed arterial spin labeling MRI reported lower mean CBF between 7 and 12 mL/100 g/min between 31 and 52 weeks postmenstrual age, mainly due to the intrinsic low signal-to-noise ratio of arterial spin labeling imaging in infants [26]. In general, CBF values were slightly higher in term compared to preterm infants [27], which is in line with our results. Additionally, preterm infants receiving mechanical ventilation had lower CBF values compared to infants with spontaneous breathing [28]. Meek et al. [29] reported that CBF increases in the first 72 h after birth in preterm infants between 24 and 31 weeks of gestation. In our cohort, term infants were usually scanned soon after birth, while preterm infants scanned around TEA were already several weeks old. This may have resulted in increasing CBF in term infants with increasing postmenstrual age, while CBF seemed fairly constant in preterm infants, independent of postmenstrual age.

From the literature, it is known that CBF depends on the amount of brain tissue and should therefore be corrected for brain size. In this study, we did not only look at CBF versus body weight, but we set out to find the best estimate of actual brain size, in order to correct CBF for brain size. This study shows significant associations between CBF and estimated brain weight at scan and 2D brain surface measurements. No significant association was found between CBF and TBV, possibly due to the small sample size (n = 89). However, we found a strong association between TBV and 2D brain surface measurements, indicating that an association between CBF and TBV is likely. In our multivariable regression model, 2D brain surface measurements at time of the MRI, head circumference or postmenstrual age at scan in combination with preterm birth were strongest predictors of total CBF. As expected, multicollinearity exists between 2D brain surface measurements, head circumference, and postmenstrual age at scan.

Several studies have described that CBF increases with increasing age and weight [3, 4]. However, we have found that, correcting for age at scan or 2D brain surface measurements, there are still differences in CBF between preterm- and term-born infants scanned at TEA. This association may be interpreted in two ways: it either indicates that prematurity may change CBF, for example due to altered growth/development of cerebral blood vessels during extra-uterine life. This is also supported by the overrepresentation of other cerebral abnormalities that are specifically related to preterm birth, such as IVH, in our preterm subgroup. We cannot exclude that relatively mild to moderate abnormalities such as IVH grade I/II or

punctate white matter lesions could affect CBF, although most of the IVH had disappeared at the time of the MRI examination. Our study did not have enough power to study this in more detail. Another explanation may be that altered CBF precedes preterm birth, possibly due to maternal (cardio)vascular changes that underlie premature delivery. Maternal risk factors, such as hypertension or pre-eclampsia, could be investigated in future research to elaborate on the etiology of differences between preterm and term infants.

This study has some limitations. First, indications to perform an MRI scan possibly differed between term infants and preterm infants. MRI scans in preterm infants were performed at TEA. At that moment, infants were generally in a stable condition. However, MRI scans of term-born infants were usually performed because of perinatal complications and performed within a few days after birth. Therefore, differences in CBF between preterm- and term-born infants could have been (partly) accounted for by differences in conditions of the infant at the time of scan. However, MRI scans with major abnormalities were excluded from this cohort to minimize differences between groups. Another limitation is the use of different sedatives during MRI as per clinical protocol in our hospital. Although both sedation methods do not result in any respiratory arrest or changes in vital signs, they may have a different effect on CBF, and among the subgroups. In order to further elucidate the differences in CBF between preterm- and term-born infants, comparative MRI studies that include unsedated healthy subjects should be undertaken. Secondly, 3D brain volume measurements were only performed in preterm infants as part of another study protocol. Possibly, associations between CBF and total brain volume are different in preterm infants compared to term-born infants. This seems unlikely, since correlations between CBF and 2D surface measurements were not significantly different between term and preterm infants.

Most studies reporting on CBF in infants include preterm infants in their first days of life or term infants with perinatal asphyxia. Little is known about CBF in healthy term infants. This study provides a reference for CBF corrected for measures of brain size in a relatively healthy cohort of preterm and term infants by the use of PC-MRA. This is a clinically easily applicable method: the sequence lasts only a few seconds, is available for multiple MRI systems and CBF measurements can be performed at the scanner, without the use of sophisticated postprocessing software.

Conclusions

In this study of relatively healthy infants at TEA without major brain abnormalities on MRI, we have demonstrated that CBF is dependent on brain size. In addition, important differences in CBF exist between preterm- and term-born infants. Combining phase-contrast magnetic resonance angiography measurements with continuous registration of cerebral perfusion/oxygenation by e.g. near-infrared spectroscopy could provide us with more insight into physiological and pathophysiological mechanisms underlying CBF in infants.

Acknowledgements

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