

Noninvasive Measurements of Regional Cerebral Perfusion in Preterm and Term Neonates by Magnetic Resonance Arterial Spin Labeling

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ABSTRACT: Magnetic resonance arterial spin labeling (ASL) at 3 Tesla has been investigated as a quantitative technique for measuring regional cerebral perfusion (RCP) in newborn infants. RCP values were measured in 49 healthy neonates: 32 preterm infants born before 34 wk of gestation and 17 term-born neonates. Examinations were performed on unsedated infants at postmenstrual age of 39–40 wk in both groups. Due to motion, reliable data were obtained from 23 preterm and 6 term infants. Perfusion in the basal ganglia (39 and 30 mL/100 g/min for preterm and term neonates, respectively) was significantly higher ($p < 0.0001$) than in cortical gray matter (19 and 16 mL/100 g/min) and white matter (15 and 10 mL/100 g/min), both in preterm neonates at term-equivalent age and in term neonates. Perfusion was significantly higher ($p = 0.01$) in the preterm group than in the term infants, indicating that RCP may be influenced by developmental and postnatal ages. This study demonstrates, for the first time, that noninvasive ASL at 3T may be used to measure RCP in healthy unsedated preterm and term neonates. ASL is, therefore, a viable tool that will allow serial studies of RCP in high-risk neonates. (*Pediatr Res* 60: 359–363, 2006)

High-risk neonates, either infants born prematurely or asphyxiated infants born at term, have a vulnerable cerebral circulation (1). Impaired autoregulation of the CBF and thus cerebral perfusion contributes to some extent to the development of brain damage in those infants (2–4). Other mechanisms, as inflammation-mediated perfusion disturbances might also be implicated in brain damage development (5), however, this point has not yet been demonstrated.

Studies of the cerebral circulation have previously been performed using different invasive methods as xenon clearance (1,6), positron emission tomography (PET) (7,8), and SPECT (9). Noninvasive approaches for estimating global CBF, *e.g.* Doppler ultrasonography and NIRS (10) have been used achieving only a limited use (11). NIRS as a cot-side method for measuring CBF was described in the late 1980s (12) but has not yet become a routine application, probably because methodological limitations are a problem in quanti-

tative NIRS perfusion measurements. However, quantitative measurements of CBF in neonates have recently been performed with sonographic flowmetry of carotid and vertebral arteries (13–16). From these studies, it is known that global CBF increases with PMA; however, quantitative regional brain perfusion data and the influence of postnatal age beyond the first 2 wk of life (16) are not yet available on healthy neonates.

In recent years, a noninvasive magnetic resonance (MR) method for accurately measuring regional brain perfusion has been developed (17). MR-Atrial spin labeling (ASL) is a completely noninvasive MR technique that enables accurate maps of RCP to be acquired in a few minutes. As this MR method is noninvasive and safe, even in very young infants, the measurements may be repeated, *e.g.* for monitoring changes in perfusion or response to treatment.

The basic principle in ASL measurements is that two images of the tissue of interest are acquired: a “tag” image in which the arterial blood has been magnetically labeled or tagged using a radiofrequency pulse and a “control” image in which the arterial blood hasn’t been labeled. The difference between the two images is perfusion weighted and if the experimental parameters are carefully controlled to fulfill a number of requirements, perfusion can be quantified using an appropriate mathematical model. A description of various ASL techniques, requirements for absolute quantification, and possible sources of error can be found in a recent review (18).

The purpose of the present study was to investigate the feasibility of ASL as a method for measuring RCP in unsedated healthy preterm infants at term equivalent age and in term neonates. Furthermore, we aimed to establish quantitative RCP values, measured by ASL, in healthy preterm infants at term-equivalent age as compared with healthy term neonates. To the best of our knowledge, this is the first study where MR-ASL has been applied for measuring RCP in healthy preterm and term neonates.

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Abbreviations: ASL, arterial spin labeling; BG, basal ganglia and thalami; CBF, cerebral blood flow; CSF, cerebral spinal fluid; GA, gestational age; GM, cortical gray matter; NIRS, near infrared spectroscopy; PMA, postmenstrual age; QUIPSS II, quantitative imaging of perfusion using a single subtraction, second method; RCP, regional cerebral perfusion; ROI, region of interest; SPECT, single photon emission computed tomography; WM, white matter

METHODS

Ethics. The local ethics committee (municipality of Copenhagen) accepted the study, and informed parental consent was obtained in all cases. No sedation was used for the MR examinations.

Subjects/study population and design. Forty-nine infants were enrolled in this ASL study. As known, normal term birth occurs between 37 and 42 wk of gestation. Thirty-two infants were born prematurely (group 1) at a median GA of 31 wk (range, 28–34 wk), median PMA at the time of MR examination was 40 wk (38–42 wk). Seventeen infants were healthy term neonates (group 2) born by elective and uneventful caesarean section at a median GA of 39 wk (37–42 wk), median PMA at the time of MR 39 wk (38–40 wk). Consequently, infants in both groups had comparable developmental ages but different postnatal ages at the time of MR examination. Of those 49 infants (32 preterm/17 term), only 29 infants (23 preterm/6 term) were included in the final results, as the rest were excluded due to excessive motion. The median postnatal age in group 1 was 9 wk (63 d) and in group 2 was 2 d. Apgar scores and umbilical cord pHs were within normal ranges for all infants. The healthy term infants were newborn infants from the nursery, born by elective cesarean section because of maternal causes as breech presentation or maternal fright. The premature infants were clinically stable throughout the neonatal period and had brain ultrasound scans without major lesions.

MR protocol. For the MR examination infants were unsedated, sleeping naturally after a feed and wrapped in blankets and a slightly deflated vacuum pillow. Padded silicone ear cups were used for noise protection. All images were acquired on a Siemens Magnetom Trio 3Tesla (T) scanner. Besides a high-resolution T₂-weighted anatomical scan, we used a proximal inversion with a control for off-resonance effects (PICORE) quantitative imaging of perfusion using a single subtraction, second method (QUIPSS II) sequence (19) for ASL-perfusion MR measurements. Fourteen to 16 slices were acquired with a slice thickness of 5 mm and 0.5 mm interslice gaps. The imaging parameters were time to QUIPSS saturation TI₁ = 700 ms, inversion time of the first slice TI₂ = 1500 ms, increase in inversion time per slice ΔTI₂ = 55.2 ms, TE (echo time) / TR (repetition time) = 23/2700 ms, FOV (field of view) = 192 mm, 64 × 64 matrix EPI (echo planar imaging) readout, giving an image resolution of 3 × 3 × 5.5 mm. The slices were positioned axially covering the entire brain and the acquisition order was ascending (inferior to superior) to reduce the required TI₂. The labeling slab was 10 cm thick and was positioned with a gap of 10 mm below the most proximal slice. The labeling slab thus covered the lower part of the head, the neck and in some cases the upper part of the chest, but not the heart. Tag and control images were acquired in an interleaved fashion with a total of 124–140 repetitions for averaging.

Postprocessing of MR-ASL data. Motion during the MR scan is a general problem with unsedated neonates and may cause severe artifacts in the acquired images, especially the perfusion-weighted ASL images. The following motion correction scheme was therefore implemented. The series of tag and control ASL images were realigned using the SPM2 (www.fil.ion.ucl.ac.uk/spm/) realignment tool (20). Periods with significant motion (more than 2 mm translation or 1.5° rotation between successive images) were identified and the images from these periods were discarded. The remaining images were realigned again and the average tag and control images were subtracted to give a mean perfusion weighted image for each subject. A threshold of at least 40 motion-free images was set to ensure adequate signal-to-noise ratio. The resulting perfusion weighted images were then inspected visually (blinded to group) for residual motion artifacts and subjects with severe artifacts were excluded. ROIs were drawn on the control images in the BG, GM, and WM. See Figure 1 for an example of such ROI. Mean perfusion values were calculated for each ROI and each subject based on the general kinetic model for ASL described in (21). Global perfusion was also calculated. T₁ of blood was assumed to be 1.5 s for perfusion quantification.

Statistical analysis. The calculated perfusion values for each ROI were compared across ROIs and groups using a two-way ANOVA. *t* Tests, corrected for multiple comparisons with a Bonferroni correction, were used to test the significance of perfusion differences between individual ROIs.

A test for homogeneity of variance (Levine's test) was performed for the three different ROIs (BG, GM, and WM) and the two groups (preterm and

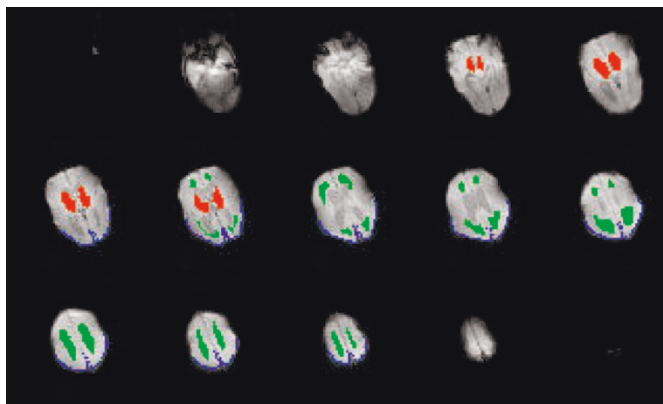


Figure 1. Axial images showing the ROIs in GM (blue), BG (red), and WM (green).

term infants) and we found that there was no statistically significant difference ($p = 0.11$) between the variances.

RESULTS

Twenty subjects were excluded due to excessive motion (9 from group 1 and 11 from group 2). For the remaining 29 subjects, 60–140 (mean, 104) images were found to be motion-free and thus contributed to the ASL images.

Figure 2 shows an example of T₂-weighted anatomical images and corresponding perfusion weighted images in 12 axial slices in one subject. Regional perfusion values were calculated in three brain areas: BG, GM, and WM. The average perfusion values are listed in Table 1 and illustrated in Figure 3.

Perfusion values in the preterm infants were significantly larger than those in the term infants. The two-way ANOVA showed significant effects of both group ($p = 0.011$) and ROI ($p < 0.0001$), but no significant interactions. There were considerable differences in regional perfusion between brain areas. Perfusion was highest in the BG, with values of 39 and 30 mL/100 g/min for the preterm and term neonates respectively. Perfusion in BG was approximately twice the value in GM ($p < 0.0001$, corrected) and approximately 2.7 times the value in WM ($p < 0.0001$, corrected). GM perfusion was slightly larger than WM perfusion, but the difference was not significant when corrected for multiple comparisons.

Global CBF (excluding CSF) values were also calculated and were found to be 21.3 mL/100 g/min for preterm infants at term-equivalent age and 16.6 mL/100 g/min for term controls (see Table 1). The difference was, however, not quite significant ($p = 0.07$).

ASL was found to be a feasible method for measuring perfusion in neonates even when they are unsedated. Motion is a substantial problem that can be solved in many cases.

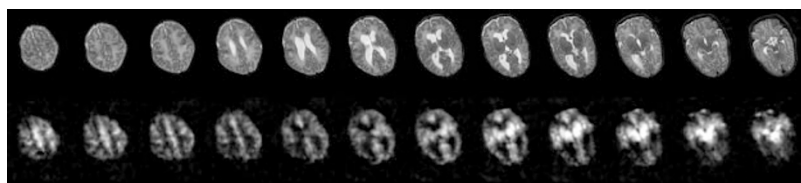
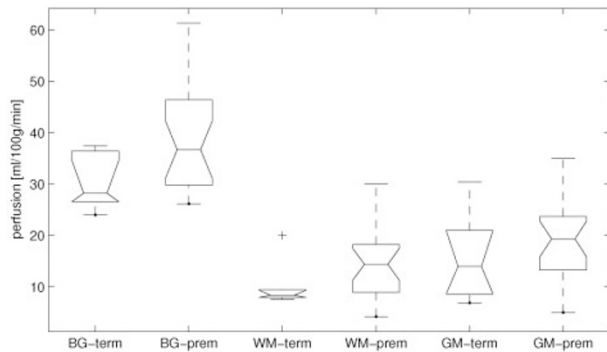


Figure 2. Anatomical T₂-weighted MR images of a 54-d-old preterm infant scanned at term (top row) and corresponding quantitative perfusion weighted images measured noninvasively using ASL (bottom row). The perfusion weighted images were reconstructed using 112 out of 124 repetitions acquired for this subject. The images from the remaining 12 repetitions were discarded due to motion.

Table 1. Absolute regional perfusion values for BG, GM, and WM as well as global perfusion measured using ASL in mL/100 g/min

Brain region	Term neonates n = 6		Preterm neonates n = 23	
	Mean	(SD)	Mean	(SD)
BG	30.2	(5.5)	38.7	(9.9)
GM	15.8	(8.8)	19.3	(7.1)
WM	10.3	(4.8)	14.8	(7.3)
Global CBF	16.6	(5.9)	21.3	(5.1)

Values are listed as mean over ROI and subjects and SD over subjects.

**Figure 3.** Box and whisker plot of the measured perfusion values (mL/100 g/min) in the premature and term neonates averaged over three brain regions: BG, WM, and GM.

Acquisition time is short (approximately 6 min). The calculated values are comparable to CBF values acquired using other methods (8,22).

DISCUSSION

The role of perfusion in the pathogenesis of brain damage in the high-risk neonate, either preterm born or asphyxiated term born infant, has been widely discussed (23,24). While evaluating cerebral perfusion in different clinical situations, it is crucial to have reliable data on healthy preterm and term infants. Furthermore, regional measurements in different brain areas provide additional information compared with global CBF measurements. Studies on high-risk neonates have been performed more than 10 y ago with the xenon-clearance method, providing values of global CBF (22). The xenon-clearance technique has the advantage of being a cot-side method, but it involves ionizing radiation. Besides, this method does not provide regional measurements of CBF. Other methods, which involve ionizing radiation, as PET (8), Xe-CT (xenon-computed tomography) (25) and perfusion CT (26), used for quantitative estimation of CBF in neonates, have also been applied. PET (8) is able to measure regional blood flow which is a great advantage. Unfortunately, PET investigations require the drawing of a substantial volume of arterial blood to quantify CBF results, which further limits its clinical use in neonates. NIRS permits quantitative estimation of the CBF (12). In spite of being a cot-side noninvasive technique, NIRS has not accomplished the primary expectations in becoming a routine bedside method because of methodological limitations. Furthermore, NIRS does not provide regional CBF measurements. Venous occlusion plethysmography (27) is another noninvasive method from which CBF

can be estimated. However, problems in interpretation of results have derived in not using it in the clinical practice in neonates.

Other techniques allow nonquantitative CBF observations, and they have been applied in neonates, as SPECT (9) and Doppler ultrasonography (28); however, SPECT does not provide absolute data but only flow distribution and it has also the disadvantage of involving ionizing radiation. Doppler ultrasonography measures cerebral blood velocity and deriving quantitative data on CBF is not feasible. Nevertheless, quantitative measurements of CBF in neonates have recently been performed with sonographic flowmetry of carotid and vertebral arteries (14). From these studies it is known that global CBF increases with PMA; however, quantitative regional brain perfusion data and the influence of postnatal age above the first 2 wk of life (16) are not yet available.

Study design. This report is based on data from a convenience sample, as we added ASL to a series of MR methods used in a study for a different purpose.

Although two ASL measurements within the same session would have been beneficial in estimating the robustness of the method, this was not possible in the majority of cases since sedation is not a routine in our hospital when studying preterm infants in research context and the duration of the scan with unsedated neonates was therefore limited by their sleep.

The ASL study was primarily designed for 1) testing the feasibility of the ASL method and 2) for establishing ASL regional perfusion values at term/term equivalent age. A secondary aim was to compare preterm and term infants who were of same PMA/developmental age but different postnatal age. Ideally, ASL measurements at multiple time-points, *e.g.* within the first few days after preterm birth, at term-equivalent age, and within the first 2 mo after term would have emphasized the effect of postnatal and developmental ages in both groups. Given the noninvasiveness of ASL, multiple measurements would definitely have been feasible. However, if the inclusion criteria of the study had been that the infants came back for a second scan 2 mo after being discharged from the hospital, probably even requiring sedation in most infants at that time, the recruitment of especially healthy controls would have been extremely difficult. And since multiple scans were not deemed crucial for the primary goals of the study, scans were only performed at one time-point. Further studies are therefore needed to corroborate the secondary findings obtained at term age in both groups.

Quantification issues. Quantification of CBF using ASL is based on using a mathematical model to relate the measured signals to CBF values. The quantitative accuracy of the PICORE QUIPSS II sequence is based on some conditions that must be fulfilled. First, TI_1 must be less than the temporal width of the bolus of labeled blood, and second $TI_2 - TI_1$ must be greater than the transit delay, *i.e.* the time it takes blood to flow from the labeling slab to the imaging slices. Previous studies (29,30) have shown that flow velocities in the basal cerebral arteries and carotid arteries are lower in neonates than in adults. It is therefore reasonable to assume that a TI_1 of 700 ms, which was optimized in adults, fulfills the above-mentioned first condition in neonates as well. There are no

direct measurements of the transit delays in neonates and the chosen value of TI_2 is also based on adult studies. If TI_2 is too short, this would violate the second condition in the lower slices or in tissue with very long transit delays and this is a limitation of the method. This often limits the accuracy of CBF measurements in WM. On the other hand, increasing TI_2 to account for long transit delays would decrease the sensitivity, especially in the upper slices, due to T_1 relaxation of the labeled blood. To reduce the effects of potentially nonoptimal TI_2 , the ROIs in this study were not drawn in the lowest or uppermost slices, but were concentrated in the central slices.

Interpretation of results. Perfusion was higher in BG than in the cortex both in preterm and in term born infants. Although the resolution of the ASL images is fairly good ($3 \times 3 \times 5.5$ mm), it is not high enough to avoid partial volume effects with CSF in the cortex. This may cause underestimation of the cortex perfusion. Although there is no CSF partial volume in the BG, there are probably some WM tracts as the internal capsule lies within the BG ROIs. Perfusion in WM is lower than in the BG and GM (14.8 and 10.3 mL/100 g/min in preterm and term infants, respectively). The validity of these numbers is, of course, based on the fulfillment of the conditions mentioned above in the previous section.

MRI is a noninvasive imaging technique. In this study, we have demonstrated that ASL is feasible for measuring perfusion in neonates, even when they are not sedated and certain movement is present in most cases. Motion is a substantial problem in this study, where 40% of infants had to be excluded for that reason. However, the motion problem can be solved in many cases (a great part of unsedated infants move a little) and the obtained perfusion values are comparable to values obtained using other known methods (8,10,12,22).

Using PET, Altman *et al.* (8) found global CBF in preterm infants (PMA = 40 wk in average) to be 5–23 mL/100 g/min (term born infants, 9–73 mL/100 g/min). Edwards *et al.* (12) found global CBF of 14–33 mL/100 g/min using NIRS (PMA = 31 wk) and Greisen *et al.* (22) found global CBF of 20 mL/100 g/min (PMA = 28–33 wk) using xenon clearance in preterm infants, too. These values are very similar to those we find in this study (21 and 16 mL/100 g/min for the preterm and term infants, respectively).

The regional CBF values reported here, especially for the preterm babies, are higher than the regional CBF-values measured by Altman *et al.* (8). However, they only calculated regional CBF in a little subgroup of sick infants where global CBF was below 10 mL/100 g/min. Furthermore, the average postnatal age in this subgroup was 8 d compared with 9 wk in our study. One might expect even lower values on the WM; however, the values we found probably reflect the high postnatal age of this group of healthy infants, compared with infants in previous studies. Our finding of relatively high WM perfusion is also reflected in a lower flow ratio between BG and WM (2.6 for preterm/3 for term infants) compared with Borch and Greisen's (9) results (4.3–5.9 for preterm infants); however, the infants in Borch and Greisen's study are younger preterm infants (median GA, 27 wk) examined early in the neonatal period, where perfusion in the WM is known to be very low.

It has recently been shown by ultrasound flowmetry that CBF volume increases continuously at least during the first 2 wk of life, suggesting that both gestational age and postnatal ages have an influence on CBF values. These findings support our results. The relatively high perfusion values we have found in the BG in both groups are also in concordance with the high metabolic rate in these areas (31).

ASL has the limitation of motion and that it is not a cot-side method, which in practice limits several repetitions in a short period of time. However, the advantage of ASL compared with other known methods is that it allows us to calculate perfusion in any chosen brain region. Specific differences in perfusion are very important while evaluating vulnerability or specific patterns of injury. In the future, when serial measurements are needed to evaluate a given clinical situation, sedation is an option which without doubt will improve ASL measurements considerably. The great routine and relatively easy availability of MR for examining neonates in many centers will permit serial ASL measurements in selected groups of infants.

In summary, our results are comparable to others; however, they are more consistent as our group is very homogeneous because all infants are healthy and they have comparable PMA. To the best of our knowledge, such a study has not been performed before.

Our study addresses new important knowledge about the regional perfusion of different brain areas in healthy neonates. The influence of preterm birth (GA and postnatal age) on cerebral perfusion is also addressed in this study by the fact that preterm infants at term equivalent age have higher regional perfusion values compared with healthy term born infants in the three brain areas studied. This fact confirms the knowledge from recent sonographic flowmetry studies that perfusion increases with postmenstrual (13,14) and postnatal (16) ages. Preterm infants were easier to examine unsedated than term-born neonates. The latter group, who were only 2 d old on average at the time of scanning, were more likely to move during the procedure, even when asleep and thereby reliable measurements were more difficult to obtain in those infants.

In summary and in spite of the limitations described above, ASL is a feasible approach for measuring brain perfusion and offers the possibility of serial investigations in high-risk neonates, such as severely asphyxiated infants, and thus the opportunity of following the progression of the regional perfusion changes eventually leading to severe brain damage (23). Improving methodological aspects is, however, needed for routine application of this method in clinical settings.

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