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Characterization of MRI techniques to assess neonatal brain oxygenation and blood flow

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Abstract

There is an increasing interest to apply physiological MRI in neonates, based on the premise that physiological parameters may provide an early biomarker of neonatal brain health and injury. Two commonly used techniques are oxygen extraction fraction (OEF) measurement using T2-Relaxation-Under-Spin-Tagging (TRUST) MRI and cerebral blood flow (CBF) measurement using phase-contrast (PC) quantitative flow MRI, which collectively provide an assessment of the brain's oxygen consumption. However, prior research has only demonstrated proof-of-principle of these methods in neonates without characterization or benchmarking of the techniques. This is because available scan time is limited in neonatal subjects, especially when performed as add-ons to clinical scans (typically less than 5 min). The work presented aims to examine the TRUST and PC MRI sequences systematically in normal neonates, through research-dedicated scan sessions. A series of characterization and optimization studies were conducted in a total of 26 radiographically normal neonates on 3 Tesla systems. Our results show that TRUST MRI at the superior sagittal sinus (SSS) provides an OEF measurement equivalent to that at the internal jugular vein (IJV) ($r=0.80$, $n=10$), yet with less scan time. Lower resolution provided better precision in the TRUST measurement ($p=0.001$, $n=9$). Therefore, the preferred OEF measurement is to apply TRUST MRI at the SSS using a spatial resolution of 2.5mm. For PC MRI, our results showed that non-gated PC MRI yielded blood flow measurements comparable to the more time-consuming gated approach in neonates ($r=0.89$, $n=7$). It was also found that blood flow could be over-estimated by 18% when imaging resolution is larger than 0.3mm ($n=7$). Therefore, non-gated PC MRI with a spatial resolution of 0.3mm is recommended for neonatal applications. In conclusion, this study verified consistency of neonatal brain oxygenation and flow measurements

across acquisition schemes and pointed to optimal strategies in parameter selection when using these sequences.

Graphical Abstract

This study aims to characterize the TRUST and phase-contrast MRI sequences for whole-brain OEF and blood flow quantification in neonates. Our results suggested that the preferred oxygenation measurement is to apply TRUST MRI at the SSS, which provided a measurement equivalent to the IJV yet with less scan time, using a spatial resolution of 2.5mm. For blood flow quantification, non-gated PC MRI with a relatively higher spatial resolution of 0.3 mm yielded results comparable to the more time-consuming gated approach.

Keywords

Oxygen extraction fraction; cerebral blood flow; Cerebral metabolic rate of oxygen; TRUST MRI; phase-contrast MRI; neonates

Introduction

Cerebral blood flow (CBF) and oxygen extraction fraction (OEF) are important physiological parameters in the neonatal brain. When combined, they provide an assessment of the brain's oxygen consumption, specifically the cerebral metabolic rate of oxygen (CMRO₂) (1). These biomarkers have significant implications in brain development (2,3) and pathological conditions in neonates, such as hypoxic ischemic encephalopathy (HIE) (4–8), hydrocephalus (9), congenital heart disease (10), and punctate white matter injury (11). Although several studies have demonstrated proof-of-principle of these measurements with MRI (7,10,12), the techniques and imaging parameters used were diverse and, more importantly, there has not been a systematic effort on sequence characterization. Despite recent advances in neonatal-specific head coils (13,14), optimization of pulse sequences for physiological imaging, which often has high signal variability and low signal-to-noise ratio

(SNR), is particularly important in neonatal MRI because of the small brain size and high susceptibility to motion in this special population.

It is pragmatically challenging to conduct technical studies in neonates. To date, most prior neonatal studies were performed on neonatal patients who had clinical indications for MRI (7,8,10,11,15,16), and the research sequences were conducted as add-ons to clinical sequences. This is because it is difficult to recruit normal neonates who would otherwise not undergo MRI to participate in MRI research studies. On the other hand, technical studies require the recruitment of normal neonates for research-dedicated sessions, so that there will be sufficient scan time to conduct systematic testing of the pulse sequence in terms of key imaging parameters and determination of test-retest reproducibility. Another benefit of performing the studies on normal neonates is that there will not be confounding factors due to pathology and medications, so the measured results will represent normative values. Therefore, in this work, we took the effort to recruit normal neonates for research-dedicated physiological MRI sessions, which to our knowledge represents a major feature of this study.

We examined two sequences relevant to the brain's oxygen homeostasis, T2-Relaxation-Under-Spin-Tagging (TRUST) MRI for the assessment of OEF and phase-contrast (PC) MRI for CBF measurement. The study focused on these two methods because they are among the most commonly used sequences for oxygenation and blood flow measurements, respectively, and both have shown some promises in neonatal applications (8,11,15). For both sequences, we characterized the dependence of the results on imaging resolution, given the considerably smaller size of the neonatal brain. Additionally, we investigated sequence-specific characteristics, i.e. consistency in oxygenation between venous vessels using TRUST MRI and consistency in blood flow between gated and non-gated PC MRI.

Materials and Methods

General

A total of 26 neonates (16 boys and 10 girls) were enrolled in this study, some of which were used in multiple sub-studies when scan time allowed. The study protocols were approved by the Institutional Review Boards of the Johns Hopkins University School of Medicine and the University of Texas Southwestern Medical Center. Informed written consent was obtained from parents of all neonates before enrollment. The mean and standard deviation of the gestational age of the recruited neonates at birth was 36.8 ± 4.4 weeks (range, 24.4 to 41.4 weeks). The mean and standard deviation of the gestational age of the recruited neonates at the time of MRI was 38.2 ± 2.3 weeks (range, 33.3 to 41.6 weeks). Babies with neurological events (such as birth asphyxia) at birth, known or suspected congenital anomalies (including congenital heart disease), chromosomal anomalies, congenital infections, or *in utero* illicit substance exposure were excluded. Infants with post-natal Grade 2 or greater intraventricular hemorrhage and/or cystic periventricular leukomalacia, both measured by cranial ultrasound, also were ineligible. Reading of the anatomic MRI scans by experienced pediatric neuroradiologists confirmed the absence of structural or signal abnormality in the neonates. None of the neonates required respiratory support at the time of scan.

Two studies were performed to characterize TRUST MRI, and two studies were performed to characterize PC MRI. All experiments were performed on 3 Tesla MRI scanners. The neonates were scanned after feeding and swaddling, without sedation. Foam padding was placed around the infant's head to minimize motion during MRI acquisition. Neonatal noise guards (MiniMuffs, Natus Pediatrics, Natus Medical Inc., San Carlos, CA) were used to minimize noise exposure. Heart rate and arterial oxygen saturation were monitored via pulse oximetry (Invivo Corporation, Gainesville, USA) throughout the MRI session. A neonatologist or a neonatology nurse practitioner was present to monitor the well-being of the neonates throughout the MRI session.

Characterization of OEF measurement

TRUST MRI separates out the pure venous blood signal from the surrounding tissue signal by magnetically labelling the venous blood and subtracting labeled images from control images (17–19). The venous blood signal then is modulated with different T2 weightings using flow-insensitive T2-preparation pulses. The monoexponential fitting of the blood signal to the T2-preparation duration [termed the effective TE (eTE)] gives the T2 value of the venous blood, which is further converted to venous oxygenation (Y_v) via pre-established neonatal-specific calibration plot (20). OEF can then be calculated as $(Y_a - Y_v)/Y_v \times 100\%$, where Y_a is arterial oxygenation measured by pulse oximetry.

In Study 1, we investigated the consistency in OEF measured by TRUST MRI in two major draining veins of the brain, the superior sagittal sinus (SSS) and internal jugular veins (IJV), in ten neonates (five boys, 37.3–41.4 gestational weeks at birth, 37.4–41.6 gestational weeks at scan) on a Siemens Skyra scanner (Siemens Healthineers, Erlangen, Germany). The imaging parameters of the TRUST scans were: repetition time (TR)=3000 ms; inversion time (TI)=1020 ms; four eTEs (0, 40, 80, and 160 ms) with a τ_{CPMG} =10 ms; acquisition voxel size=1.9×1.9×5 mm³; labeling thickness 65 mm; gap 9.8 mm. For the SSS, we acquired three pairs of control and label images at each eTE, with a scan time of 1.2 min. For the IJVs, we acquired six pairs of control and labeled images at each eTE to improve the signal-to-noise ratio (SNR) (21), with a scan duration of 2.4 min. In addition, a time-of-flight (TOF) venogram (0.2×0.2×1 mm³, 28 slices, duration of 44 s) was performed first in order to visualize the IJVs for the slice positioning of IJV-TRUST scans. Figure 1 schematically demonstrates the TRUST technique and its imaging slice positioning at SSS and IJV. In seven neonates the SSS and IJV scans were repeated as scan time allowed.

In Study 2 we evaluated the effect of in-plane resolution on TRUST measurement in nine neonates (six boys, 24.4–40.3 gestational weeks at birth, 33.3–40.4 gestational weeks at scan) on a Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands). A vacuum immobilizer was used to wrap the neonates in this study to minimize motion. Resolution values of 1.3, 1.5, 1.9, and 2.5 mm were evaluated. To focus on the resolution effect on SNR with time constraint, two eTEs, 0 and 80 ms, were used, and each eTE was acquired with six pairs of control and label images, with a scan time of 1.2 min. The imaging slice positioning and other imaging parameters were the same as the SSS scan in Study 1. For ease of comparison, the images were reconstructed with an identical voxel size (1.3×1.3×5 mm³) for all resolutions by using an identical reconstruction matrix size in the

scans. As described in Supplementary Material, a reliability index, CoV of the TRUST signal, as well as a precision index, the goodness-of-fit (ϵ_{R2}), were evaluated and compared.

Characterization of CBF measurement

PC MRI uses the phase of an image to encode the velocity of flowing spins (22,23). The velocity map is computed from the phase difference between two scans with opposite signs of bipolar gradients. The simplicity and accuracy in absolute CBF quantification as well as the relatively short scan duration have made PC MRI a practical CBF technique in neonatal applications (10,12,24,25).

In Study 3, we evaluated the consistency in blood flow measurement between cardiac-gated and non-gated PC MRI in seven neonates (five boys, 37.0–41.0 gestational weeks at birth, 37.4–41.3 gestational weeks at scan) on a Siemens Skyra scanner. For both gated and non-gated scans, the following parameters were used: single slice, TR/TE= 23/7.38 ms, flip angle (FA) =15°, voxel size=0.5×0.5×3.2 mm³, FOV=90×90×3.2 mm³, encoding velocity (V_{ENC}) = 30 cm/s. Here the V_{ENC} of 30 cm/s was selected to improve SNR at voxels near the edge of the arteries which have slow flow velocity, based on a previous study which optimized V_{ENC} for newborns (24). Since a small V_{ENC} may cause phase wrapping in the voxels with flow velocity higher than V_{ENC} , velocity aliasing correction was performed before further analysis when needed. The non-gated scan resulted in one velocity map, with 3 averages and scan duration of 13 s. The gated scan results in 20 images at different cardiac phases with scan duration of 2–3 min depending on the neonate's heart rate. ECG signal was used for cardiac gating. The imaging slice of the PC scans was oriented perpendicular to an internal carotid artery (ICA) in each subject at the level of the foramen magnum, following previous literature (12,24).

In Study 4, we evaluated the effects of imaging resolution and number of averages in seven neonates (four boys, 37.0–40.4 gestational weeks at birth, 37.4–40.7 gestational weeks at scan) on a Siemens Skyra scanner. Unlike the TRUST sequence, the PC MRI velocity map is susceptible to partial voluming due to its TOF effect. Because the TOF effect suppresses the static tissue signal while enhancing the flowing signal, voxels at the edge of the blood vessels that partially contain flowing blood would be counted as voxels that fully contain flowing blood, which could lead to biases in CBF estimation. In this regard, higher imaging resolution is expected to provide a more accurate CBF measurement. However, higher spatial resolution is usually associated with lower sensitivity and longer scan duration. In addition, more number of averages for the PC MRI acquisition is also expected to provide better accuracy but increases scan time. Therefore, an optimal tradeoff between accuracy and time efficiency needs to be determined for a practical PC-MRI protocol in neonates. In this study, three spatial resolutions, 0.3, 0.4 and 0.5mm, in combination with three numbers of averages 3, 6 and 9, were examined using non-gated PC MRI. Scan durations were 13, 18, and 29 s for the resolution of 0.5, 0.4, and 0.3 mm with 3 averages, 26, 36 and 58 s for the resolution of 0.5, 0.4, and 0.3 mm with 6 averages, and 40, 55 and 87 s for the resolution of 0.5, 0.4, and 0.3 mm with 9 averages, respectively. Other imaging parameters were identical to the non-gated PC MRI used in Study 3. For ease of comparison, the images were reconstructed with an identical voxel size (0.3×0.3×3.2 mm³) for all resolutions by using an

identical reconstruction matrix size in the scans. CBF analysis was similar to that in Study 3. The effects of PC MRI imaging resolution and number of averages on CBF quantification were evaluated.

Data analysis

Data analysis was performed using in-house Matlab scripts (MathWorks, Natick, MA). Analysis of the TRUST data followed methods previously reported (19,26,27). After motion correction, pairwise subtraction of control and label images was performed to create difference images, which yielded pure blood signals. Next, a preliminary region of interest (ROI) was manually drawn on the difference image at eTE of 0 ms to include the vessel of interest (26,27). Six voxels with the highest signals in the ROI were chosen as the final mask for spatial averaging. The averaged blood signals (3 and 6 averages at each eTE for the SSS and IJV, respectively) were fitted to a mono-exponential function to obtain a R_2 (i.e., $1/T_2$) estimate, which was then converted to Y_v via a calibration plot established for neonates (20). For this conversion, the hematocrit value was assumed to be 0.40 in females and 0.42 for males for neonates without a hematocrit measure in their medical record. Otherwise, neonate-specific hematocrit values were used. For Study 1, the larger one of the left and right IJVs was used for better SNR. OEF was calculated as $(Y_a - Y_v)/Y_v \times 100\%$, where Y_a is arterial oxygenation measured by pulse oximetry. Mean and coefficient of variance (CoV) of OEF at the SSS and at the IJV were calculated and compared. For Study 2, CoV of the TRUST signal was calculated for each resolution as the standard deviation of ROI-averaged signal intensity divided by the mean signal across six dynamics at eTE of 0ms. We also evaluated the effect of resolution on the precision of TRUST measurements by comparing the goodness-of-fit (ϵ_{R_2}) (18), i.e., standard error of the R_2 estimation giving the same fitting condition across resolutions.

Data processing of PC MRI followed previously reported methods (24,28). First, velocity aliasing correction was performed when phase wrapping was observed in the targeted artery (usually in the center of the artery) on the velocity map (29). Next, the rater (P.L., with 9 years of experience of PC MRI ROI drawing) manually drew an ROI on the magnitude image by tracing the boundary of the targeted artery based on the brightness of the voxels without including adjacent vessels. The blood velocity can then be converted to blood flow by integrating over the artery ROI (30). The resulting blood flow was in units of ml/min, i.e., blood influx per unit time. The total blood flow to the brain, as a summation of blood flow from all feeding arteries, can further be converted to CBF in units of ml/100g/min after normalization to brain parenchyma volume. Since we focused on within-subject comparisons of ICA flow in Studies 3 and 4, blood flow in ml/min was reported without normalizing to the subjects' brain volume fed by ICA.

Statistical tests

Considering the sample size, non-parametric statistical tests were used in this study. Regression analysis and paired Wilcoxon signed-rank test were performed to compare the TRUST-OEF measurement between the SSS and IJV locations, and compare the PC-flow measurement between cardiac-gated and non-gated acquisitions. To compare data across resolutions, Friedman tests with repeated measures of resolution were performed on CoV of

TRUST signal, goodness-of-fit (ϵ_{R2}) of TRUST R2 fitting, and PC-flow. If a resolution effect was observed in the Friedman test, paired Wilcoxon signed-rank tests among the resolutions were conducted. With the optimal resolution, blood flow data across number of averages were also compared using Friedman test and post-hoc paired Wilcoxon signed-rank test. A $p < 0.05$ was considered statistically significant.

Results

In Study 1, OEF was found to be $31.81 \pm 4.11\%$ and $32.84 \pm 3.77\%$ for SSS and IJV measurements, respectively, with no significant difference detected. As shown in Figure 2, OEF measured at these two locations showed significant correlation with each other ($y = 0.97x$, $r = 0.80$, $p = 0.005$), demonstrating good consistency of the two measurements. CoV of the OEF measurement was slightly higher at the IJV ($13.98 \pm 9.58\%$) than at the SSS ($5.61 \pm 5.50\%$), although this difference was not significant. These results suggest that compared to IJV, a TRUST measurement at the SSS can reliably assess global OEF with shorter scan duration and without an extra venogram for positioning.

Results of Study 2 are shown in Figure 3. Friedman analysis showed that the imaging resolution has a significant effect on CoV of the TRUST signal ($p = 0.02$) and ϵ_{R2} of the R2 estimation ($p = 0.02$). Post hoc pairwise comparisons showed that the 1.3mm resolution yielded significantly higher CoV ($p < 0.03$) and ϵ_{R2} ($p < 0.05$) than the other resolutions. No significant differences in CoV and ϵ_{R2} were found among the other 3 resolutions. However, linear mixed effect analysis revealed that there is a significant association between resolution and ϵ_{R2} ($p = 0.001$), where lower resolution tended to yield lower ϵ_{R2} (i.e., more precise R2 estimation), suggesting that the resolution of 2.5mm may be a good choice for a TRUST scan in neonates. No significant age effect was found on CoV of the TRUST signal and ϵ_{R2} of the R2 estimation at any resolution ($p > 0.12$ and $p > 0.42$, respectively).

Figure 4a shows an example of PC MRI images from the non-gated scan of one neonate. Unlike in adult scans, no obvious pulsation artifact was observed in these non-gated images. Figure 4b shows the corresponding blood flow measurement from this neonate. Blood flow varied during a cardiac cycle, but the mean value was close to the non-gated result. Regression analysis of all neonates showed a strong correlation between the gated and non-gated blood flow (Figure 4c; slope = 0.99, $r = 0.89$, $p = 0.007$). Since cardiac-gated PC MRI is thought to be most accurate in blood flow quantification, our result suggests that non-gated PC MRI may be a time-efficient choice of accurate blood flow quantification in neonates.

Figure 5a and b shows the magnitude and velocity maps of the nine resolution/average combinations in one neonate. Since larger number of averages provides better SNR (and thus, a more accurate blood flow measurement), we first focused on the results from 9 averages to evaluate the effect of imaging resolution (Figure 6a). A Friedman test with repeated measures revealed significant effect of imaging resolution on blood flow ($p = 0.02$). Post-hoc analysis showed that both 0.4 and 0.5mm significantly overestimated CBF by 18% when compared to 0.3mm ($p = 0.02$ and $p = 0.03$, respectively). Next, we focused on the results from 0.3mm resolution and compared different number of averages (Figure 6b). A Friedman test showed no significant difference among the three numbers of averages used

($p=0.16$), suggesting that with 3 averages is the time efficient choice for accurate blood flow quantification.

Discussion

The present study aimed to characterize the TRUST and PC MRI sequences for whole-brain OEF and blood flow quantification in neonates. Our results suggest that the preferred oxygenation measurement is the TRUST MRI at the SSS, which provides a measurement equivalent to the IJV, with less scan time, using a slightly lower spatial resolution than previously used value. For blood flow quantification, non-gated PC MRI with a relatively higher spatial resolution of 0.3 mm yielded results comparable to the more time-consuming gated approach. With these settings, the entire scan for a complete CMRO2 dataset in neonates, which include one 1.2 min TRUST scan at the SSS and four 1 min PC scans at the four feeding arteries of the brain, will be 5.5 min.

The present study has several novel aspects. First, to our knowledge, the present study is the first to systematically characterize imaging sequences for CMRO2 quantification in neonates. Previous studies had demonstrated the feasibility of *in vivo* CMRO2 measurements in newborns (7,10,12), but none of the existing methods have been examined in terms of the effects of key imaging parameters on the measurement results. Another novel aspect is that the present study was conducted on normal neonatal subjects in research-dedicated physiological MRI scan sessions. Virtually all prior neonatal physiological MRI studies were performed on neonatal patients as add-ons to clinical sequences. While scanning on clinical patients is the ultimate goal of most MRI research, at the stage of technical development it is more desirable to have research scan sessions on normal neonates. This is because time is often limited for add-on scanning in the clinical MRI session, precluding the opportunity of test-retest evaluation or performing multi-scan comparisons. Pathological conditions and medications of the sick babies could also confound the functional and physiological MRI results. Therefore, in this study, significant effort was made to recruit normal neonates, which made the above-mentioned sequence characterization and optimization feasible. The importance of having a research-dedicated session is further underscored by the fact that, in our institution and in many other institutions around the world, neonates of several days old are scanned without using sedation. Therefore, this factor further limits the scan time available in this special population that is highly susceptible to motion, and our study design of a research-dedicated physiological MRI session is a worthy effort.

To measure global CMRO2, one of the two key factors is the measurement of global OEF. With tools like TRUST MRI available, the first challenge is determining the appropriate anatomic location of the measurement. Although it is plausible to measure global OEF at the IJVs (which drains 79% of the total blood from the brain (21)), IJV measurement is limited by the requirement of an additional venogram to visualize the IJVs (which requires additional scan time) and the proximity to sinus and bone structures which lead to field inhomogeneity and low SNR. In contrast, SSS scans can be positioned on a standard localizer image without an additional venogram. Our results showed that OEF values measured at the SSS and IJV are highly consistent in normal neonates, which is in

agreement with previous reports in healthy adults (21,27). Since the scan duration at the SSS is only half of that at the IJV, while the precision is comparable, if not better at the SSS than at the IJV, TRUST measurement at SSS is recommended to be used to assess global OEF in neonatal patients, including those with global brain function change and damage. However, in patients with localized CMRO₂ change, global OEF measurements may not be sensitive enough to detect the localized change, and regional measurement techniques, such as vessel-specific or voxelwise OEF mapping (31–33), needs to be developed for neonates.

Since lower resolution yielded more precise OEF estimation, an in-plane resolution of 2.5mm is recommended for TRUST scans in neonates. This resolution is much lower than that required by other global OEF techniques available in neonates, such as 0.85 mm used in MR susceptometry (10), and 1.25 mm used in T2-Prepared-Tissue-Relaxation-Inversion Recovery (T2-TRIR) method (7). This is because the TRUST sequence can automatically isolate pure blood signal via the control and label subtractions, rather than relying on a processing operator to manually select a ROI of pure blood as in the other two techniques. Therefore, TRUST sequence is not affected by partial voluming effects, and can afford a lower imaging resolution to increase SNR.

As for CBF quantification, a cardiac-gated PC scan is often thought to provide an accurate measurement of CBF (25). Although a few studies have suggested that non-gated PC MRI can provide comparable CBF measurements as cardiac gated scans in adults, none have evaluated the accuracy of non-gated PC MRI in neonates. Since the SNR of PC MRI in neonates is low, it is unknown whether additional reduction in SNR caused by pulsatile flow may lead to a bias in CBF quantification using non-gated PC MRI in neonates. Our results revealed that the non-gated PC MRI scan in neonates is not affected by the pulsatile flow, and could provide blood flow measurements consistent with the cardiac-gated scan while taking only 1/10 of the scan time. In addition, in neonates, pulse oximetry measurements from probes placed on their feet, which is typically used on fingers to provide cardiac triggering in adults, may not always provide reliable tracing due to foot movement even when the baby is in natural sleep. Hence, an ECG setup is needed when cardiac-gated scanning is performed in neonates, which causes additional preparation effort. Therefore, non-gated PC MRI is a time-efficient approach to provide accurate CBF measurements in neonates where short scan duration is highly preferred.

Unlike the TRUST sequence, the partial voluming effect is a main challenge of the PC MRI acquisition. The partial voluming effect arises at the edge of a vessel lumen where the voxels contain signals from both moving spins and stationary tissue. Given the limited resolution of the acquired image, partial voxels that contain only part of the blood vessel are considered as full voxels in the vessel ROI, which will lead to an overestimation in the cross-sectional area of the vessel and thus in CBF values calculated as the integration of flow velocity within the cross-sectional area (30). Therefore, lower imaging resolution is expected to be more affected by partial voluming, which has been demonstrated in adults (28). Our data demonstrated an 18% overestimation of neonatal blood flow in PC MRI scans acquired at 0.4 and 0.5 mm resolutions, compared to that acquired at 0.3 mm resolution. Several previous studies have reported CBF measurements in neonates using PC MRI with low imaging resolutions, such as 1 mm (10), 0.6 mm (25), and 0.5 mm (11,12,24). Therefore,

our results suggest that interpreting literature values of CBF acquired with low PC resolutions should be done with an abundance of caution regarding overestimation.

The findings from the present study need to be interpreted in the context of its limitations. First, the optimal TRUST and PC MRI parameters proposed in this work for whole brain CMRO2 quantification in neonates have not applied to large-scale studies. Given the limited sample size used, non-parametric statistical tests were utilized, but multiple comparison corrections were not performed. Therefore, a larger-scale study needs to be performed in the future to improve the statistical power and assess the feasibility of the optimized neonatal CMRO2 protocol in a larger population. Second, due to local clinical regulations, the neonates in studies 1, 3 and 4 were scanned without a vacuum immobilizer or sedation, unlike some other studies (7,12). Therefore, motion may have confounded our results and could explain the higher CoV of OEF measurements in Study 1 than in a previous report in which a vacuum immobilizer was used (12). Better strategies to reduce motion in subject preparation, as well as the adoption of motion-adaptive acquisitions (34), would benefit future studies. The utilization of a neonatal-specific head coil also would reduce head motion and increase SNR. The development of an automatic algorithm that can reject motion-affected TRUST control/label pairs, similar to that developed in ASL (35), would also improve the OEF measurements. Third, in the PC MRI data analysis, only manual ROI selection was performed in this work. Although several previous studies have shown excellent inter-rater reliability ($r > 0.98$) in tracing the boundary of the arteries on the PC MRI images in both neonates (12,24) and adults (21,28), the rater's skill and experience may affect the accuracy of the PC MRI results. In future studies, we will work on a rater-independent automatic segmentation method to extract the cross-sectional area of the arteries.

In conclusion, this work conducted a series of characterization and optimization studies to benchmark two commonly used physiological MRI sequence for the assessment of brain oxygenation and blood flow in radiographically normal neonates. The results demonstrated consistency of the measurements and also pointed to optimal strategies of parameter selection when using these sequences. Our findings suggest that it is feasible to obtain whole-brain CMRO2 assessment in neonates without needing contrast agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CBF	cerebral blood flow
CMRO2	cerebral metabolic rate of oxygen
CoV	coefficient of variation

CPMG	Carr–Purcell–Meiboom–Gill
eTE	effective TE
FOV	field of view
HIE	hypoxic–ischemic encephalopathy
ICA	internal carotid artery
IJV	internal jugular vein
OEF	oxygen extraction fraction
PC	phase-contrast
SNR	signal-to-noise ratio
SSS	superior sagittal sinus
TI	inversion time
TOF	time-of-flight
TR	repetition time
TRUST	T2 relaxation under spin tagging
Y_a	arterial oxygenation
Y_v	venous oxygenation

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Figure 1.

Illustration of the TRUST MRI technique and the position of the imaging slices on the venous sinuses. (A) Example of TRUST results from one neonate. The difference between control and label images yields pure venous blood signal, which was then modulated by different T2-weighting. The venous T2 was obtained by mono-exponential fitting of the blood signals at 4 eTEs, and then converted to Y_v using a pre-established T2-Y calibration. (b) Positioning of the TRUST imaging slice (blue bar) on the superior sagittal sinus (SSS). (c) Positioning of the TRUST imaging slice (blue bar) on the internal jugular veins (IJV, indicated by red arrows).

Figure 2. Scatter plot of OEF values obtained from the SSS and IJV (N=10). Each dot represents one neonate. Black line indicate linear fitting ($y=0.97x$).

Figure 3. Comparisons of TRUST results across different in-plane resolutions (N=9). (a) Resolution effect on TRUST signals. (b) Resolution effect on the goodness-of-fitting (ϵ_{R2}) of the TRUST T2 estimation. Error bars indicate standard error.

Figure 4.

Results from the cardiac-gated and non-gated PC MRI scans. (a) Magnitude and velocity maps from a non-gated scan. Arrows indicate the internal carotid artery (ICA, targeted artery of the scan), external carotid artery (ECA) and vertebral artery (VA). (b) Blood flow from the gated and non-gated scans from one neonate. Red dash line indicates the mean flow of the gated scan. (c) Scatter plot between the gated and non-gated blood flow measurements across 7 subjects. Each dot represents one neonate. The black line indicate linear fitting ($y=0.99x$). The dashed line indicates the line of unity.

Figure 5. PC MRI images of 9 resolution/average combinations from a representative neonate. (a) Magnitude images. The images were zoomed in with the targeted ICA in the center (red arrow). (b) The corresponding velocity maps.

Figure 6. The effects of in-plane resolution and number of averages on PC MRI (N=7). (a) The dependence of blood flow on resolution. (b) The dependence of blood flow on the number of averages. Error bars indicate standard error.