Quantitative Susceptibility Mapping of Venous Vessels in Neonates with Perinatal Asphyxia

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ABSTRACT

BACKGROUND AND PURPOSE: Cerebral venous oxygen saturation can be used as an indirect measure of brain health, yet it often requires either an invasive procedure or a noninvasive technique with poor sensitivity. We aimed to test whether cerebral venous oxygen saturation could be measured using quantitative susceptibility mapping, an MR imaging technique, in 3 distinct groups: healthy term neonates, injured term neonates, and preterm neonates.

MATERIALS AND METHODS: We acquired multiecho gradient-echo MR imaging data in 16 neonates with perinatal asphyxia and moderate or severe hypoxic-ischemic encephalopathy (8 term age: average, 40.0 [SD, 0.8] weeks’ gestational age; 8 preterm, 33.5 [SD, 2.0] weeks’ gestational age) and in 8 healthy term-age controls (39.3 [SD, 0.6] weeks, for a total of n = 24. Data were postprocessed as quantitative susceptibility mapping images, and magnetic susceptibility was measured in cerebral veins by thresholding out 99.95% of lower magnetic susceptibility values.

RESULTS: The mean magnetic susceptibility value of the cerebral veins was found to be 0.36 (SD, 0.04) ppm in healthy term neonates, 0.36 (SD, 0.06) ppm in term injured neonates, and 0.29 (SD, 0.04) ppm in preterm injured neonates. Correspondingly, the derived cerebral venous oxygen saturation values were 73.6% (SD, 2.8%), 71.5% (SD, 7.4%), and 72.2% (SD, 5.9%). There was no statistically significant difference in cerebral venous oxygen saturation among the 3 groups (P = .751).

CONCLUSIONS: Quantitative susceptibility mapping–derived oxygen saturation values in preterm and term neonates agreed well with values in past literature. Cerebral venous oxygen saturation in preterm and term neonates with hypoxic-ischemic encephalopathy, however, was not found to be significantly different between neonates or healthy controls.

ABBREVIATIONS: \( \chi \) = magnetic susceptibility; \( \text{CSaO}_2 \) = cerebral arterial oxygen saturation; \( \text{CSvO}_2 \) = cerebral venous oxygen saturation; \( \text{Hct} \) = hematocrit; HIE = hypoxic-ischemic encephalopathy; NIRS = near-infrared resonance spectroscopy; QSM = quantitative susceptibility mapping; SSS = superior sagittal sinus; TRUST = T2-relaxation-under-spin tagging

Perinatal asphyxia is the condition resulting from the deprivation of oxygen to a neonate and can lead to brain tissue damage or death. Asphyxia at birth can affect virtually any organ, but the brain is of the highest concern because it is the least likely to quickly or completely heal.1 Hypoxic-ischemic encephalopathy (HIE) occurs when the entire brain is deprived of an adequate supply of oxygen and can result in neurologic disability, such as cerebral palsy, mental retardation, and epilepsy. HIE occurs in 1.5 per 1000 live births2 and is the fifth leading cause of death worldwide in children younger than 5 years of age (8%).3

Currently, the severity of HIE is mainly assessed by clinical parameters and conventional MR imaging and can be classified into mild, moderate, or severe categories.4,5 While identifying HIE in term infants is generally well-characterized, its identification in preterm infants remains complex, with variable inclusion criteria being discussed and reported.6-9 More accurate markers would be useful...
for detection, classification, early therapeutic interventions, and predictors of long-term outcome. Several studies have investigated various alternative methods for measuring HIE, such as DWI, MR spectroscopy, urinary nuclear MR metabolomic profiling, and visual evoked potentials, with varying levels of reported success.

Unfortunately, the 2 current methods for measuring CSvO2 increased CSvO2. Thus, QSM, a noninvasive method, may provide blood compared with the surrounding brain tissue will indicate a “luxury perfusion” state, suggesting serious brain damage. Normal CSvO2 values, meanwhile, would suggest intact coupling between CBF and metabolic needs. Thus, knowing the CSvO2 in preterm and term infants who are suspected of having HIE could provide clinicians with invaluable information. Unfortunately, the 2 current methods for measuring CSvO2 require either the invasive insertion of an internal jugular vein catheter for co-oximetry or a blood gas analyzer, or the noninvasive use of near-infrared resonance spectroscopy (NIRS). NIRS, however, has been shown to have poor sensitivity at low CSvO2 compared with co-oximetry and can reach a depth of only a few millimeters.

Quantitative susceptibility mapping (QSM) examines gradient-echo phase data, usually acquired with SWI, to determine local tissue magnetic susceptibility (χ). Because deoxyhemoglobin in the venous blood is paramagnetic, a decrease in χ of venous blood compared with the surrounding brain tissue will indicate increased CSvO2. Thus, QSM, a noninvasive method, may provide an indirect measure of CSvO2. For example, Doshi et al, in 2015, reported increased CSvO2 in adults following mild traumatic brain injury. Similarly, Chai et al, in 2017, reported increased CSvO2 in subjects with mild traumatic brain injury compared with healthy controls, but they also reported a positive correlation of CSvO2 with postconcussive symptoms. Chai et al, in 2020, also reported reduced CSvO2 in patients undergoing hemodialysis, which also correlated with cognitive scores (r = 0.492, P = .02).

Thus, we set out to determine how well CSvO2 could be measured using QSM and hematocrit (Hct) from blood samples in term and preterm neonates with moderate or severe HIE and to compare those values with those of healthy term controls. We hypothesized that after perinatal asphyxia, both preterm and term neonates with moderate or severe HIE would demonstrate increased CSvO2 through decreased cerebral vein magnetic susceptibility compared with healthy term controls.

**MATERIALS AND METHODS**

**Patients**
Between January 2017 and January 2018, preterm and term neonates with a clinical history of perinatal asphyxia and moderate or severe HIE who were transferred to Children’s Hospital of Chongqing Medical University intensive care nursery were enrolled in a study evaluating the detection of brain injury by MR imaging, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Recruitment and scanning ended due to the neonatal ward of the hospital moving to a new branch of the hospital, where their scanners were from a different vendor, and there were no Philips Healthcare scanners. The institution’s Committee on Clinical Research Ethics approved the study protocol, and informed consent was obtained from the parents. The inclusion criteria were determined on the basis of the definition of perinatal asphyxia and moderate or severe HIE as follows: 1) evidence of perinatal asphyxia (Apgar score of ≤ 7 for >5 minutes after birth or a history of acute perinatal event, placental abruption, cord prolapse, or the need for ventilation for at least 10 minutes after birth); 2) evidence of moderate or severe HIE distinguished by using the Sarnat and Sarnat clinical stages for term infants and infants between 33 and 37 weeks’ gestation and significant changes in neurologic examination findings and/or seizures for infants younger than 33 weeks gestation; and 3) abnormal MR imaging findings in all patients on T1-weighted, T2-weighted, and FLAIR images, mainly but not only in the basal ganglia/thalami region, watershed region, and periventricular white matter caused by HIE.

Subjects were sedated using 5 mg/kg of phenobarbital (intramuscular injection). Neonates with high motion or image artifacts were excluded. In total, 8 term neonates and 8 preterm neonates who were determined to have perinatal asphyxia and moderate or severe HIE were included for further study. Eight term neonates with hyperbilirubinemia who were free of other neonatal complications, such as congenital and chromosomal abnormalities and with normal MR imaging findings were recruited prospectively as healthy controls. Hct values were obtained as part of the regular clinical work-up.

**MR Imaging Acquisition**
Brain MR images were obtained on a 3T system (Achieva; Philips Healthcare) using an 8-channel sensitivity encoding head coil. Data for QSM were collected using a 3D gradient-echo sequence with 5 echoes (TR = 30 ms, TE1 = 4.5 ms, echo spacing = 5.5 ms, flip angle = 17°, FOV = 196 × 154 × 103 mm³, acquired voxel size = 0.50 × 0.5 × 1.0 mm³, reconstructed voxel size = 0.5 × 0.5 × 0.5 mm³, scan time = 5 minutes 9 seconds). Other scans included the following: inversion recovery turbo spin-echo T1-weighted (TR/TE = 7000/600 ms, TE = 15 ms, section thickness = 5 mm, FOV = 160 × 151 × 98 mm³, acquisition matrix = 220 × 163, scan time = 2 minutes 17 seconds); turbo spin-echo T2-weighted (TR = 5000 ms, TE = 100 ms, section thickness = 5 mm, FOV = 160 × 149 × 98 mm³, acquisition matrix = 332 × 205, scan time = 1 minute 38 seconds); and fast FLAIR images (TR/TE = 12,000/2850 ms, TE = 140 ms, section thickness = 5 mm, FOV = 160 × 149 × 98 mm³, acquisition matrix = 176 × 144, scan time = 3 minutes 55 seconds). The total acquisition time was 13 minutes 23 seconds.

**MR Imaging Analysis**
QSM images of all 5 echoes were postprocessed from the phase data of the multi-gradient-echo scans. Phase unwrapping was achieved using a 3D Laplacian algorithm, while the background field was removed using the variable sophisticated harmonic artifact reduction for phase method. A Gaussian filter (σ = 0.5) was applied to the normalized field maps to smooth out high-frequency errors originating from the reconstruction steps before
the inversion. A 2-step dipole inversion algorithm was used to solve the dipole inversion problem. The last echo was used to obtain the brain mask, which effectively removed the external cerebral veins. Using the last echo to generate the brain mask reliably removed artifacts from air-tissue and bone-tissue interfaces, eg, sinuses, especially in the later echoes, without the need for manual erosion. This QSM algorithm can be freely accessed at https://github.com/kamesy/QSM.m. Finally, only the fourth echo (TE = 21 ms) was used for measuring \( x \) values because even echoes were flow-compensated along the readout direction and the second echo (TE = 10 ms) had a poor contrast-to-noise ratio.

The \( x \) of cerebral veins was measured by thresholding out the lowest 99.95% values of the whole brain. In the absence of intracranial hemorrhage and because neonates have very low brain iron content, voxels that reside entirely inside veins reflect the structures with the highest magnetic susceptibility values. Total blood volume is about 3%. Venous blood volume is about two-thirds of total blood volume. For a voxel to be free of partial volume effects and given the spatial resolution of 0.5 \( \times \) 0.5 \( \times \) 1 mm\(^3\) of the scan, only veins with an inner diameter of at least 1 mm could be included in the analysis. After thresholding, images were assessed by A.M.W. to ensure that only veins remained (Fig 1). The remaining 0.25% of \( x \) values was then averaged to give the mean cerebral \( x \) value for each subject. ROIs were also drawn manually on nonvein tissue by A.M.W. to calculate \( \Delta X \). Visual inspection did not reveal any germinal matrix bleeding in the deep cerebral veins.

**Calculating CSvO\(_2\)**

CSvO\(_2\) was calculated using the following equation:

\[
\Delta X = \Delta X_{do} \times HCT \times (1 - CSvO2),
\]

where \( \Delta X \) is the susceptibility difference between venous blood and surrounding tissue, \( \Delta X_{do} \) is the susceptibility difference per unit hematocrit between fully deoxygenated and fully oxygenated blood, Hct is the individual fractional hematocrit, and CSvO\(_2\) is the blood oxygen saturation. \( \Delta X_{do} \) was taken to be \( 4 \times \pi \times 0.21 \), or 2.64 ppm.\(^{37,38}\)

**Statistical Analysis**

Statistical analysis was performed using R 3.4.2 (2017; http://www.r-project.org/). The relationship between calculated CSvO\(_2\) and condition (healthy control, preterm injury, and term injury) was investigated using a 1-way ANOVA. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality.

**RESULTS**

**Patient Characteristics**

Demographic data and clinical characteristics for both groups (8 healthy controls, 8 term neonates, and 8 preterm neonates with perinatal asphyxia and moderate or severe HIE) are summarized in Table 1. No significant differences were found in gestational age, corrected gestational age at MR imaging, time interval between age at birth and age at MR imaging, birth weight, or sex between healthy controls and term neonates with HIE. No significant differences were found in sex, time interval between age at birth and age at MR imaging, clinical history, and symptoms and signs between term neonates and preterm neonates with perinatal asphyxia and moderate or severe HIE. As expected, a significant difference (\( P < .05 \)) was found in the Apgar grade between healthy term neonates and term neonates with HIE. Between term and preterm neonates with HIE, significant differences (\( P < .05 \)) were found only in gestational age, corrected gestational age at MR imaging, and birth weight, as would be expected.

**CSvO\(_2\) Analysis**

The mean \( x \) value of the internal cerebral veins in healthy controls and term and preterm injured neonates was found to be 0.36 (SD, 0.04) ppm, 0.36 (SD, 0.06) ppm, and 0.29 (SD, 0.04) ppm, respectively, while the mean fractional Hct values were 0.52 (SD, 0.03), 0.49 (SD, 0.07), and 0.42 (SD, 0.06), respectively. Correspondingly, the derived mean CSvO\(_2\) values were 73.6% (SD, 2.8%), 71.5% (SD, 7.4%), and 72.2% (SD, 6.0%), respectively. The Cohen D effect size between each group was found to be 0.38 for healthy controls and term injured neonates; 0.30 for healthy controls and preterm neonates; and 0.10 between term injured neonates and preterm.
neonates. A CSvO₂ boxplot among the 3 groups with individual points for each subject is shown in Fig 2. One-way ANOVA analysis did not reveal that the condition (healthy control, preterm injury, and term injury) made a significant difference among groups ($P > .05$). Boxplots of $\chi$ and Hct values in each group, with individual points for each subject are included in the Online Supplementary Data.

### DISCUSSION

In this study, we quantified CSvO₂ from $\chi$ values in the internal cerebral veins of preterm and term neonates with HIE and healthy term controls. Moderate-to-severe HIE caused by intrapartum or late antepartum hypoxic-ischemic events may lead to neurodevelopmental disability. It is of great importance to examine cerebral hemodynamic changes in neonates with moderate or severe HIE because this examination may lead to a better understanding of the cerebral oxygen metabolism of brain injury in HIE and early therapeutic interventions. Although no statistical difference in CSvO₂ values was found between healthy term controls and preterm and term infants with moderate or severe HIE, to the best of our knowledge, this is one of the first studies measuring CSvO₂ using QSM in healthy term neonates, as well as the first to do so in term and preterm neonates with moderate or severe HIE. Thus, our reported values for healthy neonates as well as injured preterm and term neonates may be used in future studies for comparison purposes. These values agree well with previously reported values using other methods (Table 2).

Noninvasive measurements of CSvO₂ in neonates has historically been quite difficult. The current best practice, NIRS, does not provide robust and reliable measurements due to several limitations, including contamination from extracerebral tissue,
They reported a mean CSvO2 of 67% (SD, 7%) in the supratentorial region.

De Vis et al.20 also obtained CBF measurements and found injured subjects to have significantly increased CBF postinjury. Along with the susceptibility-based methods of measuring CSvO2, there have been other MR imaging–related techniques worth mentioning. One such method is known as T2-relaxation-under-spin tagging (TRUST). For instance, Shetty et al.21 in 2019, reported CSvO2 changes during and after therapeutic hypothermia in neonatal HIE using TRUST. The CSvO2 was calculated by measuring 1/T2 (R2) of the SSS. They examined CSvO2 values during early hypothermia treatment (18–24 hours after initiating treatment) and after and found posttreatment CSvO2 to have been reduced from 73.2% (SD, 9.4%) (during treatment) to 68.5% (SD, 9.6%) (posttreatment). These posttreatment values agreed well with a previous study that reported 62.6% (SD, 8.3%) in healthy infants using the same method.22 While these initial reports of measuring CSvO2 using TRUST are promising, some drawbacks should be considered. On the one hand, the measurement of R2 is relatively easier to postprocess than QSM because it requires only a few simple steps. On the other hand, unlike QSM, the measurement of R2 has confounding factors such as fat, fibrosis, and edema,23 along with saturation and blooming artifacts. Additionally, the scan required for QSM provides a wealth of additional information such as R2* maps and SWI, which can be used to better characterize lesions.24 In fact, SWI is already often used in clinical settings to detect intracranial hemorrhages and other brain abnormalities and is often part of the neonatal and pediatric MR imaging protocols.25,26 The scan is fast (<3 minutes on modern scanners) even at high spatial resolution (≤1 mm3). Disadvantages in QSM include a range of different approaches for background field removal, dipole inversion, and referencing to other tissue.

The results of our study indicate that CSvO2 values were not found to be significantly different in injured preterm and term neonates compared with healthy term controls. One reason for this finding could be that preterm and term infants with moderate or severe HIE could have reduced CBF, which, along with a reduced oxygen metabolism, would result in CSvO2 similar to that in healthy controls. In this case, injured neonates would have reduced oxygen metabolism and, thus, compromised brain health. To test these 2 opposing theories, however, we would require additional information, such as CBF and cerebral arterial oxygen saturation (CSaO2). For instance, the oxygen extraction and arterial blood (generally 30% but can vary considerably among subjects)27 and an insensitivity to low CSvO2 levels.28 QSM, meanwhile, is a relatively new technique, which fully quantifies the CSvO2 in healthy fetuses (Table 2).46,47

Along with the susceptibility-based methods of measuring CSvO2 in neonates and fetuses, there have been other MR imaging–related techniques worth mentioning. One such method is known as T2-relaxation-under-spin tagging (TRUST). For instance, Shetty et al.21 in 2019, reported CSvO2 changes during and after therapeutic hypothermia in neonatal HIE using TRUST. The CSvO2 was calculated by measuring 1/T2 (R2) of the SSS. They examined CSvO2 values during early hypothermia treatment (18–24 hours after initiating treatment) and after and found posttreatment CSvO2 to have been reduced from 73.2% (SD, 9.4%) (during treatment) to 68.5% (SD, 9.6%) (posttreatment). These posttreatment values agreed well with a previous study that reported 62.6% (SD, 8.3%) in healthy infants using the same method.22 While these initial reports of measuring CSvO2 using TRUST are promising, some drawbacks should be considered. On the one hand, the measurement of R2 is relatively easier to postprocess than QSM because it requires only a few simple steps. On the other hand, unlike QSM, the measurement of R2 has confounding factors such as fat, fibrosis, and edema,23 along with saturation and blooming artifacts. Additionally, the scan required for QSM provides a wealth of additional information such as R2* maps and SWI, which can be used to better characterize lesions.24 In fact, SWI is already often used in clinical settings to detect intracranial hemorrhages and other brain abnormalities and is often part of the neonatal and pediatric MR imaging protocols.25,26 The scan is fast (<3 minutes on modern scanners) even at high spatial resolution (≤1 mm3). Disadvantages in QSM include a range of different approaches for background field removal, dipole inversion, and referencing to other tissue.

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Table 2: Comparison of CSvO2 percentages in fetuses and neonates in the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>CSvO2 (mean, %)</th>
<th>Method</th>
<th>Subjects</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Hoeven et al</td>
<td>73.56 (SD, 4.25)</td>
<td>Fiber optic catheter</td>
<td>Healthy neonates</td>
<td>Frontotemporal region</td>
</tr>
<tr>
<td>Buchwald et al</td>
<td>64.12 (SD, 4.6)</td>
<td>NIRS</td>
<td>Healthy neonates</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>Wintemark et al</td>
<td>77.3 (SD, 4.7)</td>
<td>NIRS</td>
<td>Hypothermia therapy (moderate) in neonatal HIE</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>Wintemark et al</td>
<td>77.6 (SD, 6.6)</td>
<td>NIRS</td>
<td>Hypothermia therapy (severe) in neonatal HIE</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>De Vis et al</td>
<td>65.0 (SD, 13.0)</td>
<td>T2-TRIR</td>
<td>Healthy neonates</td>
<td>SSS</td>
</tr>
<tr>
<td>Shetty et al</td>
<td>73.2 (SD, 5.5)</td>
<td>TRUST</td>
<td>Hypothermia therapy in neonatal HIE</td>
<td>SSS</td>
</tr>
<tr>
<td>Shetty et al</td>
<td>68.5 (SD, 9.6)</td>
<td>TRUST</td>
<td>Post-hypothermia therapy in neonatal HIE</td>
<td>SSS</td>
</tr>
<tr>
<td>Liu et al</td>
<td>62.6 (SD, 8.3)</td>
<td>TRUST</td>
<td>Healthy neonates</td>
<td>SSS</td>
</tr>
<tr>
<td>Yadav et al</td>
<td>67 (SD, 7)</td>
<td>QSM</td>
<td>Healthy fetuses (~31 wk)</td>
<td>SSS</td>
</tr>
<tr>
<td>Jain et al</td>
<td>55.2</td>
<td>Susceptometry</td>
<td>Neonates with congenital heart disease</td>
<td>SSS</td>
</tr>
<tr>
<td>Yadav et al</td>
<td>62.6 (SD, 3.25)</td>
<td>Susceptometry</td>
<td>Healthy fetuses (~31 wk)</td>
<td>SSS</td>
</tr>
<tr>
<td>Neelavalli et al</td>
<td>66 (SD, 9.4)</td>
<td>Susceptometry</td>
<td>Healthy fetuses (~34 wk)</td>
<td>SSS</td>
</tr>
<tr>
<td>Average</td>
<td>68.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: T2-TRIR indicates T2-prepared tissue relaxation inversion recovery; SSS, superior sagittal sinus; TRUST, T2-relaxation-under-spin tagging; QSM, quantitative susceptibility mapping; NIRS, near infrared resonance spectroscopy.
fraction, the percentage of oxygen used from the blood as it passes through the capillary network, can be calculated by subtracting the fraction of oxygen saturation in the cerebral arteries (CSaO2) from the fraction of oxygen saturation in the cerebral veins (CSvO2). While CSaO2 can be easily and noninvasively measured using a pulse oxygen monitor and CBF can be acquired using another MR imaging scan such as arterial spin-labeling or phase contrast, our study, unfortunately, did not acquire these data because they were not part of the original study design. Thus, we cannot make more conclusive statements regarding preterm and term injured brain health. An alternative explanation could be because our data show premature rupture of fetal membranes in >60% of the preterm infants, which is higher than usual. It is possible that these infants have adapted to the outside world and have CSvO2 values closer to term infants.

Two strengths of our method are as follows: The QSM algorithm is available for free on-line at https://github.com/kamesy/QSM.m for researchers and clinicians to download and use. Furthermore, our method of selecting venous susceptibility values (looking at the highest 0.25%) helps reduce human error using a completely data-driven process.

There are several limitations to the current study. Only 8 subjects from each group were examined, limiting our statistical power. We did not acquire CSaO2 or CBF measurements, which would have allowed us to examine why both preterm and term infants with moderate or severe HIE did not show statistically significant differences in CSvO2 compared with healthy controls. Furthermore, no follow-up with these patients was attempted, such as cognitive scores, which could have been used to investigate any correlations with CSvO2. In the future, we hope to add more subjects, acquire CSaO2 and CBF measurements (such as arterial spin-labeling), and perform cognitive measurements as the infants develop later in life. One piece of advice the authors wish to pass on to future researchers is the importance of acquiring and using Hct values in calculating CSvO2. Had we used a constant value for Hct, the preterm group would have been found to have a statistically significant difference in CSvO2. However, by using acquired Hct from each subject, this difference was no longer seen because Hct increases with gestational age and preterm infants were scanned at a younger gestational age.

CONCLUSIONS
We were able to measure CSvO2 in the internal cerebral veins in healthy term, preterm, and term injured neonates. These values agree well with previously reported values in the literature. However, we did not see a difference in CSvO2, despite the presence of HIE in the term injured and preterm infants. More studies should be performed in preterm and term infants with moderate or severe HIE, while acquiring other brain oxygen metrics such as CBF and CSaO2 along with cognitive metrics as the infants develop later in life.

REFERENCES


