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ABSTRACT

BACKGROUND AND PURPOSE: Children with sickle cell disease have low hematocrit and elevated CBF, the latter of which can be assessed with arterial spin-labeling MR imaging. Quantitative CBF values are obtained by using an estimation of the longitudinal relaxation time of blood ($T1_{blood}$). Because $T1_{blood}$ depends on hematocrit in healthy individuals, we investigated the importance of measuring $T1_{blood}$ in vivo with MR imaging versus calculating it from hematocrit or assuming an adult fixed value recommended by the literature, hypothesizing that measured $T1_{blood}$ would be the most suited for CBF quantification in children with sickle cell disease.

MATERIALS AND METHODS: Four approaches for $T1_{blood}$ estimation were investigated in 39 patients with sickle cell disease and subsequently used in the CBF quantification from arterial spin-labeling MR imaging. First, we used 1650 ms as recommended by the literature ($T1_{blood}$-fixed); second, $T1_{blood}$ calculated from hematocrit measured in patients ($T1_{blood}$-hematocrit); third, $T1_{blood}$ measured in vivo with a Look-Locker MR imaging sequence ($T1_{blood}$-measured); and finally, a mean value from $T1_{blood}$ measured in this study in children with sickle cell disease ($T1_{blood}$–sickle cell disease). Quantitative flow measurements acquired with phase-contrast MR imaging served as reference values for CBF.

RESULTS: $T1_{blood}$-measured (1818 $\pm$ 107 ms) was higher than the literature recommended value of 1650 ms, was significantly lower than $T1_{blood}$-hematocrit (2058 $\pm$ 123 ms, $P < .001$), and, most interesting, did not correlate with hematocrit measurements. Use of either $T1_{blood}$-measured or $T1_{blood}$–sickle cell disease provided the best agreement on CBF between arterial-spin labeling and phase-contrast MR imaging reference values.

CONCLUSIONS: This work advocates the use of patient-specific measured $T1_{blood}$ or a standardized value (1818 ms) in the quantification of CBF from arterial spin-labeling in children with SCD.

ABBREVIATIONS: ASL = arterial spin-labeling; Hct = hematocrit; pCASL = pseudocontinuous ASL; PC-MRI = phase-contrast MR imaging; SCD = sickle cell disease; $T1_{blood}$ = longitudinal relaxation time of blood

Sickle cell disease (SCD) is associated with a considerable risk of stroke,[1] which is reduced by blood transfusion therapy[2] and identified by screening blood flow velocities in intracranial arteries with transcranial Doppler.[3] Additionally, microvascular tissue perfusion, or CBF, is also increased in patients with SCD[4,5]; which is related to low hematocrit (Hct).[6,7] CBF measurements are instrumental in understanding the pathophysiology of impaired perfusion in the occurrence of silent cerebral infarcts in SCD.[4,8,9] Noninvasive CBF measurements can be performed with arterial spin-labeling (ASL) and a quantification model to calculate physiological CBF values. The wide range of CBF values reported in the literature in SCD[1,4,9] emphasizes the need for either more accurate estimates or direct measurements of the often-assumed parameters required for CBF quantification models.

The longitudinal relaxation time of the blood ($T1_{blood}$) parameter accounts for the decay of the ASL signal with time, and

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From the Department of Radiology (L.V., D.F.R.H., C.B.L.M.M., H.J.M.M.M., A.J.N.), Academic Medical Center, Amsterdam, the Netherlands; Department of Pediatric Hematology (V.v.d.L., K.J.F.), Emma Children's Hospital, Academic Medical Center, Amsterdam, the Netherlands; C.J. Gorter Center for High Field MRI (M.J.P.v.O.), Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; Department of Pediatric Hematology (M.H.C.), Erasmus University Medical Center–Sophia Children's Hospital, Rotterdam, the Netherlands; Department of Biomedical Engineering (A.B.), Viterbi School of Engineering, University of Southern California, Los Angeles, California; Department of Pediatrics (J.C.W.), Children's Hospital Los Angeles, Los Angeles, California; and Sunnybrook Research Institute (H.J.M.M.M.), Toronto, Ontario, Canada.

Patients were recruited and scanned by V.v.d.L., H.J.M.M.M., and D.F.R.H.; the study was designed by K.J.F. and A.J.N. The data were analyzed by L.V. and H.J.M.M.M, and the final manuscript was drafted, reviewed, and edited by all authors.

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Please address correspondence to Lena Václavů, MSc, Department of Radiology, Z0-178, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands; e-mail: l.vaclavu@amc.uva.nl

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inaccurate estimates of $T1_{blood}$ could result in over- or underestimation of CBF.[10-12] For healthy adults, with a stable Hct, a fixed $T1_{blood}$ value of 1650 ms is recommended for CBF quantification from pseudocontinuous ASL (pCASL) at 3T.[13,14] $T1_{blood}$ is inversely correlated with Hct,[10,13,15-19] and a linear relationship has been proposed in the literature permitting the calculation of $T1_{blood}$ from measured Hct values.[12,13,16] While Hct ranges from 38% to 45% in healthy children,[20] it is as low as 18%–30% in children with SCD.[21] Hence, if measured Hct values are available, $T1_{blood}$ can be derived accordingly. However, recent studies suggest that $T1_{blood}$ may additionally differ in children with SCD.[12,22,23]

Owing to recent developments in MR imaging, direct measurements of the inversion recovery of $T1_{blood}$ are now possible by combining a global inversion pulse and a subsequent section-selective Look-Locker readout in the sagittal sinus.[16,17] Patient-specific, in vivo $T1_{blood}$ measurements are noninvasive, robust, and fast, making them preferable to calculating $T1_{blood}$ from blood samples. Our first hypothesis was that in vivo–measured $T1_{blood}$ would be higher in children with SCD than the adult reference value of 1650 ms due to anemia. We also considered that conformational changes inherent to sickle red blood cells may produce additional unforeseen changes in $T1_{blood}$.[12] We investigated the importance of measuring patient-specific differences in $T1_{blood}$ for the accuracy of ASL quantification in patients with SCD. We hypothesized that patient-specific $T1_{blood}$ values acquired in vivo would improve CBF quantification in SCD compared with CBF quantification with $T1_{blood}$ calculated from Hct or $T1_{blood}$-fixed at 1650 ms.

The aim of this study was to determine which of the following 4 $T1_{blood}$ derivatives would provide the best CBF quantification compared with quantitative reference CBF values measured with 2D phase-contrast MR imaging (PC-MRI): 1) literature-recommended adult $T1_{blood}$ of 1650 ms,[14] 2) $T1_{blood}$ calculated from Hct, 3) in vivo–measured $T1_{blood}$, or 4) a fixed average SCD value from the mean $T1_{blood}$ measured in vivo in this study.

MATERIALS AND METHODS

Experiments were performed according to principles of the Declaration of Helsinki, and the study was approved by the local institutional review board at the Academic Medical Center, Amsterdam, the Netherlands.

Patients

Eligible children were approached prospectively from 2 outpatient clinics as described previously.[24] Informed consent was obtained from parents or guardians and children older than 12 years of age. Inclusion criteria were HbSS or HbSβ^0 genotypes and 8–17 years of age. Exclusion criteria were a history of stroke, stenosis of the intracranial arteries and velocity of >155 cm/s on transcranial Doppler imaging, current chronic blood transfusion therapy, bone marrow transplant, MR imaging contraindications, and major concomitant health problems. Patients were in a steady-state of SCD, without evidence of infection or sickle cell crisis up to 1 month before participation.

Hematocrit

Venous blood samples were drawn from an antecubital vein on the day of the MR imaging assessment and processed according to standard procedures in the hospital laboratory. Hct values were used to calculate $T1_{blood}$-Hct values.

Table 1: Demographic and clinical characteristics

Demographic or Clinical Parameter	Mean and SD
Total No.	39
Females (No. and % of total)	16 (41%)
Males (No. and % of total)	23 (59%)
Age (yr)	12 ± 2
Hematocrit (%)	23 ± 3
Hemoglobin (g/d/L)[a]	8.4 ± 1.1
Hemoglobin F (%)[b]	10 ± 6
Hemoglobin A2 (%)[c]	4.8 ± 1
Hemoglobin S (%)	84 ± 5
Mean corpuscular volume (mL)[d]	82 ± 10
Mean corpuscular hemoglobin concentration (mmol/L)[e]	21 ± 0.6

[a] Normal range reference values: Hb = 10–16.
[b] HbF < 1%.
[c] HbA2 = 2–3.
[d] MCV = 75–95.
[e] MCHC = 19.0–22.5.

MR Imaging Acquisition

Thirty-two children underwent 3T imaging on an Intera scanner (Philips Healthcare, Best, the Netherlands) with an 8-channel head coil, and due to a scanner upgrade, the remaining 8 children were scanned at 3T on an Ingenia (Philips Healthcare) with a 15-channel head coil. The protocol included 3D-TOF MRA, 2D T2-weighted, $T1_{blood}$, 2D pseudocontinuous ASL, and 2D phase-contrast sequences.

The $T1_{blood}$ acquisition section was planned perpendicular to the posterior sagittal sinus[16] and comprised a multi time-point inversion recovery experiment. This technique uses a global inversion pulse followed by a series of 95° section-selective readout pulses, which are intended to saturate the tissue surrounding the sinus. Assuming complete replenishment of inverted blood between 2 consecutive pulses, a high contrast is achieved between tissue and blood, allowing the detection of the inversion recovery of blood. A nonselective adiabatic 180° inversion pulse (hyperbolic secant pulse, B1 value/duration of the pulse = 13.5 mT/13 ms) preceded a single section Look-Locker EPI readout (flip angle, 95°; voxel size, 1.5 × 1.5 mm; matrix, 240 × 240 mm; section thickness, 2 mm; TE/TR, 15/10,000 ms; TI_1, 200 ms; ΔTI, 150 ms; 60 readouts; 6 signal averages; scan duration, 1 minute 20 seconds).

A gradient-echo single-shot EPI pCASL sequence was used to acquire perfusion-weighted images (75 subtracted label-control pairs; resolution, 3 × 3 × 7 mm; FOV, 240 × 240 mm; 17 continuous axial sections; TE/TR, 17/4000 ms; flip angle, 90°; labeling duration, 1650 ms; postlabeling delay, 1525 ms; background suppression, 1680 and 2830 ms after a prelabeling saturation pulse; scan duration, 10 minutes 7 seconds).

Quantitative flow measurements were obtained with a nontriggered 2D single-section PC-MRI acquisition in the internal carotid and vertebral arteries. Imaging parameters were the following: FOV, 230 × 230 mm; voxel size, 0.45 × 0.45 mm; TR/TE, 15/5 ms; flip angle, 15°; maximum velocity-encoding, 140 cm/s; section thickness, 4 mm; scan duration, 1 minute.

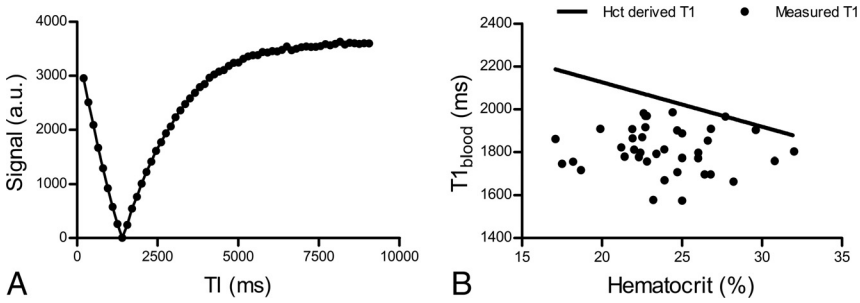

FIG 1. *A*, Representative inversion recovery of the venous TI_{blood} signal acquired in the sagittal sinus in a child with sickle cell disease. *B*, In vivo–measured TI_{blood} values are significantly lower than Hct-derived TI_{blood} values. TI_{blood}-measured does not correlate with patient hematocrit (mean Hct, 23% ± 3%) (Pearson $r = 0.02$, $P = .89$; $n = 39$).

Table 2: TI_{blood} values and corresponding CBF values quantified from ASL[a]

TI_{blood}	Method (Value)	ASL-CBF (mL/100 g/min)	*P* Value
TI_{blood}-fixed	Literature (1650 ms)	114 ± 13	<.05
TI_{blood}-Hct	Calculated from patient's hematocrit (variable)	95 ± 10	<.05
TI_{blood}-measured	Measured with MR in vivo in patients with SCD (variable)	106 ± 14	NS
TI_{blood}-SCD	Mean of TI_{blood}-measured (1818 ms)	105 ± 12	NS

Note:—NS indicates not significant.

[a] Repeated-measures ANOVA was performed to test the significance (*P* in the final column) of differences between CBF from ASL and reference CBF obtained from phase-contrast MRI flow measurements.

Data Postprocessing

TI_{blood}. Blood-filled voxels within the sagittal sinus were selected on the basis of the highest signal intensity. Voxel values were subsequently averaged, and the data were fitted to a 3-parameter model (Nealder-Mead method; MathWorks, Natick, Massachusetts), with the parameters M_0, Offset, and $T1_{blood}$,[17] and solved for $T1_{blood}$:

$$1)\quad M(nTI) = abs\left(M_0 \times \left[1 - 2 \times \exp\left(-\frac{\text{Offset} + TI_1 + (nTI - 1) \times \Delta TI}{T1_{blood}}\right)\right]\right),$$

where M models the T1 recovery from the data, nTI is the readout number, *abs* denotes the absolute values, M_0 is the net magnetization, "Offset" accounts for imperfect inversion, TI_1 is 200 ms, and ΔTI is the sampling interval (150 ms). The sum of squared errors of the final (optimal) iteration after solving the Nealder-Mead function indicated how well the data fitted the model and served as a quality check.

Cerebral Blood Flow. Raw pCASL data were processed as described previously[25] by using a processing pipeline for the registration and quantification of the data. A 2-compartment quantification model was used, as published in detail previously[9,26] (except that the equilibrium magnetization of arterial blood was derived from the M_0 of CSF multiplied by the blood-water partition coefficient,[27] and labeling efficiency was 0.7). The $T1_{blood}$ parameter was adjusted for each CBF quantification as follows: first, adult fixed $T1_{blood}$ of 1650 ms taken from literature[13]; second, patient-specific Hct-calculated $T1_{blood}$ values[16]; third, patient-specific in vivo–measured $T1_{blood}$ values; and finally an average $T1_{blood}$ value obtained from the mean of in vivo $T1_{blood}$ measurements in our patients with SCD. $T1_{blood}$-Hct was calculated per patient according to the relationship proposed by Varela et al[16] derived from venous blood in neonates:

$$2)\quad T1_{blood} = \frac{1}{0.5 \times \text{Hct} + 0.37}.$$

PC-MRI. The internal carotid and vertebral arteries were segmented manually from phase difference images by using ITK-SNAP (http://www.itksnap.org) to obtain total flow (milliliters per minute). Total flow was then divided by brain mass (gram), which was calculated from the product of the volume (estimated from segmented anatomic images in SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and an assumed brain density of 1.05 g/L,[28] to obtain PC-MRI CBF in milliliters/100 g/min,[29] which served as the reference value for CBF.[22,29]

Statistical Analysis

A Pearson correlation was performed between $T1_{blood}$-measured and Hct. Repeated-measures ANOVA was used to test the statistical significance of the differences among the 5 CBF quantification methods: 1) CBF ($T1_{blood}$-fixed at 1650 ms), 2) CBF ($T1_{blood}$-Hct), 3) CBF ($T1_{blood}$-measured in vivo, 4) CBF ($T1_{blood}$-SCD fixed at the average measured value), and 5) PC-MRI reference CBF. Paired *t* tests were used to test the statistical significance of individual group differences post hoc. Agreement between PC-MRI and the 4 ASL methods was investigated with linear regression and Bland-Altman analyses in Matlab (MathWorks, Natick, Massachusetts). Linear regression analysis was performed to show agreement between PC-MRI and the 4 CBF quantification methods from ASL. Bland-Altman analysis was performed to indicate the bias corresponding to over- or underestimation of the ASL CBF method compared with the PC-MRI method. The limits of agreement (dotted lines) indicate the 95% confidence intervals.

RESULTS

Demographic and clinical characteristics are summarized in Table 1. One patient's $T1_{blood}$ scan was discarded due to poor image quality, so the mean CBF values from pCASL are based on 39 datasets. For PC-MRI, only 33 datasets were of sufficient quality to quantify reference CBF.

Measured TI_{blood}

The mean Hct was 23% ± 3% for 39 children. The mean $T1_{blood}$-measured value was 1818 ± 107 ms, which was significantly lower than mean $T1_{blood}$-Hct values (2045 ± 69 ms; paired *t* test, $P < .001$) but higher compared to the fixed adult value of 1650 ms. $T1_{blood}$-measured was not significantly different between scanners (*t* test, $P = .94$). Figure 1*A* shows a representative inversion recovery curve from 1 patient as a function of the sum of least-squares fit. The sum of squared errors from fitting the $T1_{blood}$-measured values to the model is shown in On-line Fig 1. $T1_{blood}$-measured values did not correlate

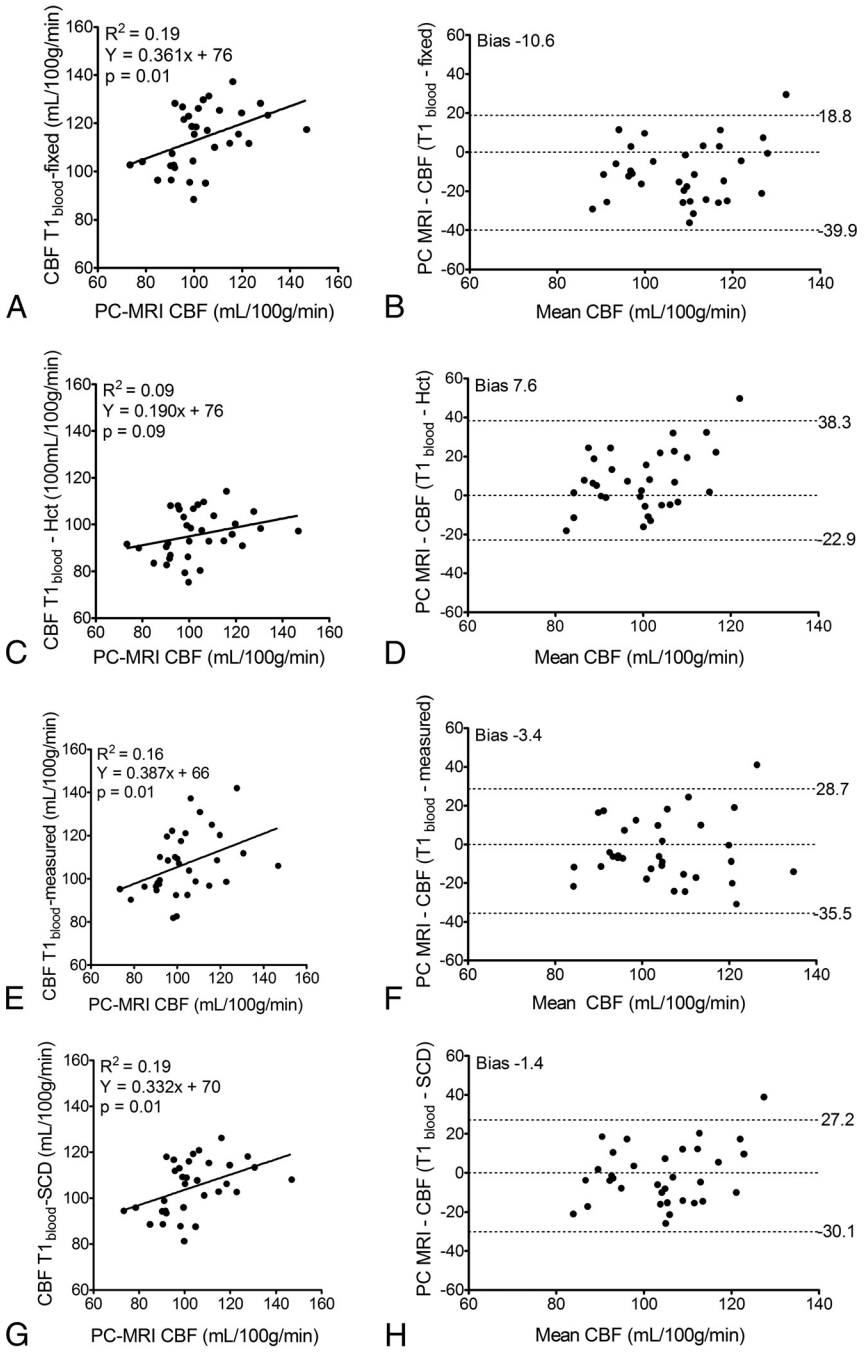

FIG 2. Linear regression and Bland-Altman plots between CBF values measured with PC-MRI and ASL, which was quantified by using 4 different TI_{blood} values: a fixed literature value of 1650 ms (CBF TI_{blood}-fixed) (*A* and *B*); TI_{blood} calculated from hematocrit (CBF TI_{blood}-Hct), TI = 0.5*Hct+0.37 (*C* and *D*)[16]; in vivo–measured TI_{blood} (CBF TI_{blood}-measured) (*E* and *F*); and a fixed SCD value obtained from the mean of the in vivo–measured TI_{blood} (CBF TI_{blood}-SCD) (*G* and *H*). The left panel shows linear regressions (*solid line*), and the right panel shows the mean on the x-axis versus the difference on the y-axis between pCASL and PC-MRI CBF with limits of agreement (*dotted lines* above and below) ($n = 33$).

with Hct values measured from blood samples ($r = 0.02$, $P = .89$; Fig 1*B*) or with age ($r = 0.03$, $P = .85$) and did not differ significantly between males and females (*t* test, $P = .37$).

Cerebral Blood Flow

Four CBF quantification methods were compared with PC-MRI CBF, the results of which are summarized in Table 2. Linear regression analyses between PC-MRI and pCASL CBF are shown in the left panel of Fig 2 and reveal slopes significantly different from zero for all CBF quantifications except for the $T1_{blood}$-Hct CBF quantification. The Bland-Altman plots in the right panel of Fig 2 show the bias and limits of agreement for the mean and the difference between the measurements. $T1_{blood}$-fixed overestimated CBF and $T1_{blood}$-Hct underestimated CBF, while the individual in vivo $T1_{blood}$-measured values and mean $T1_{blood}$-SCD value provided the best agreement with PC-MRI values, both on an absolute level, revealed by no significant difference between PC-MRI and CBF in the repeated-measures ANOVA analysis (Table 2), but also on a one-to-one basis, as demonstrated in the linear regression plots (Fig 2). A representative example of CBF maps quantified with $T1_{blood}$-measured from 2 patients is shown in Fig 3.

DISCUSSION

We demonstrate that in vivo–measured venous $T1_{blood}$ values in children with SCD were higher than the literature-recommended 1650 ms, were not significantly correlated with measured Hct, and were lower than the Hct-derived values for $T1_{blood}$. CBF quantified with in vivo–measured $T1_{blood}$ provided better agreement with PC-MRI reference measurements than CBF quantified with fixed adult $T1_{blood}$ and Hct-derived $T1_{blood}$.

TI_{blood} and Hematocrit

Previous literature suggests that healthy children 6–18 years of age (assuming a stable Hct of 40%–45%) have $T1_{blood}$ values between 1680 and 1880 ms.[18] In this study, in patients with a much lower Hct than healthy children, we measured $T1_{blood}$ values closer to the upper range of the literature-reported $T1_{blood}$ values.[18] Yet, our $T1_{blood}$ values were lower than expected, considering the low Hct values obtained from our patients' blood samples. It is unlikely that we underestimated $T1_{blood}$ due to sequence-related limitations because the Look-Locker T1 technique has previously provided robust results in the same ROI.[16,17,27]

Reports of $T1_{blood}$ values ranging from 1500 to 2100 ms follow a linear relationship with Hct between 23% and 50%.[13,16,18] It is possible that we did not have sufficient precision to detect this inverse relationship in our dataset or that the range of Hct values

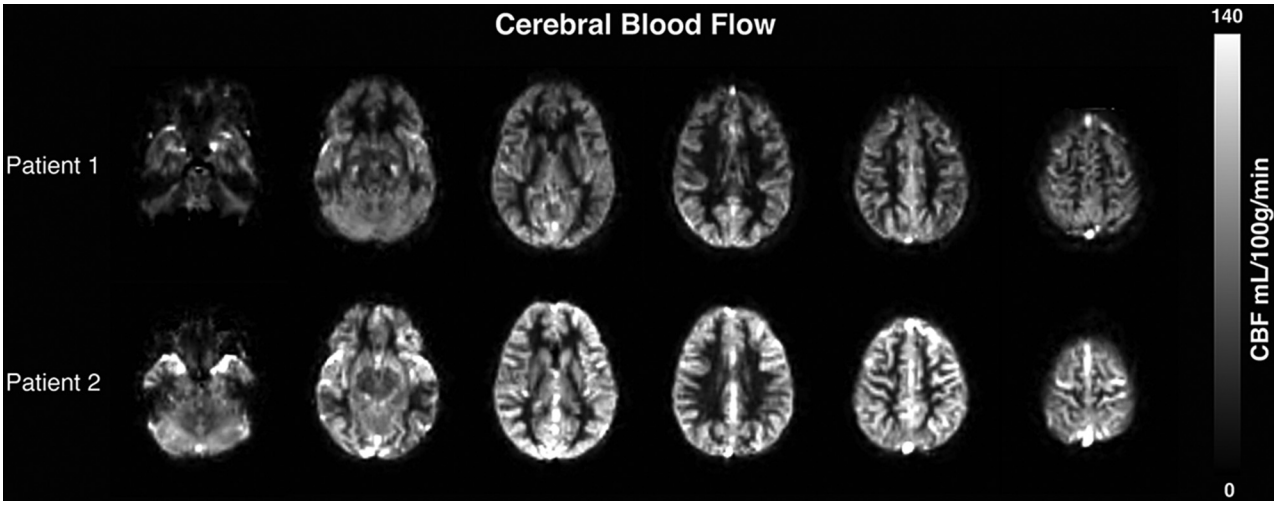

FIG 3. Axial brain sections showing CBF from 2 representative examples of 2 fourteen-year-old boys with SCD. The upper row shows a patient with low CBF and the lower row shows a patient with high CBF.

was too narrow in our patients (17%–32%). Abnormalities in SCD blood, other than low Hct, may account for the incongruity between $T1_{blood}$ and Hct measured here. While we did not measure blood rheology, abnormalities such as decreased red blood cell deformability, increased aggregation, and increased viscosity have been demonstrated consistently.[21,30-34] Furthermore, red blood cells in SCD exhibit different membrane properties and viscosity, which may have reduced $T1_{blood}$ due to shrinkage of cells and therefore lower water content.[35]

CBF Quantification

Our CBF results fall within the large range of reported values in children with SCD (~70–150 mL/100 g/min).[1,4,9,36,37] The necessary reliance on a quantification model for obtaining physiologically meaningful CBF values means that the method is sensitive to the assumptions of the model used, which could differ between healthy adults and children with SCD. The fact that measured $T1_{blood}$ ameliorates the CBF quantification but Hct-calculated $T1_{blood}$ does not opposes the use of Hct-corrected CBF quantification in SCD and, instead, advocates the use of measured $T1_{blood}$. $T1_{blood}$ measurements are advantageous over Hct-calculated $T1_{blood}$ because they are faster (1 minute 20 seconds) and less invasive. In the absence of $T1_{blood}$ measurements, we propose using a mean value of 1818 ms, as measured in this study in children with SCD, which would suffice in improving the absolute agreement with PC-MRI for CBF quantification from ASL.

Limitations

This study should be considered in light of the technical limitations of the $T1_{blood}$ measurement and the potentially inaccurate reference flow measurements from PCMR.

Whereas $T1_{blood}$ measurements were acquired in venous blood, the quantification model requires arterial estimates. However, because we compared venous $T1_{blood}$ measurements with $T1_{blood}$ values derived from venous Hct, the potential mismatch would have been similar for both methods. Moreover, we demonstrate that the measured venous $T1_{blood}$, used to quantify CBF, improved the agreement with independently acquired flow measurements in arterial vessels with PC-MRI, which shows that although the arterial measurement may be better, the venous measurement is sufficient.

PC-MRI as a surrogate for CBF could be critiqued for CBF overestimation due to partial volume effects[38] and inaccurate brain density estimates or underestimated flow due to noncardiac-triggered acquisition. Still, recent literature suggests that errors in flow values associated with nontriggered 2D PC-MRI are <3% compared with triggered acquisitions.[29,39] Despite these limitations, a recent study has shown high agreement (intraclass correlation coefficient, 0.73) between PC-MRI and pCASL,[40] emphasizing that PC-MRI is currently the best noninvasive reference for pCASL CBF.

CONCLUSIONS

Inaccurate $T1_{blood}$ estimates can be a major confounder for quantitative perfusion assessment from ASL. Patient-specific, in vivo–measured $T1_{blood}$ measurements provided more accurate CBF values than $T1_{blood}$ derived from Hct values. To avoid overestimation of CBF in SCD, we recommend the use of a fixed value of 1818 ms ($T1_{blood}$-SCD) for CBF quantification from ASL in SCD if measured $T1_{blood}$ values are not available.

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