In Vivo T1 of Blood Measurements in Children with Sickle Cell Disease Improve Cerebral Blood Flow Quantification from Arterial Spin-Labeling MRI


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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 (T1blood). Because T1blood depends on hematocrit in healthy individuals, we investigated the importance of measuring T1blood in vivo with MR imaging versus calculating it from hematocrit or assuming an adult fixed value recommended by the literature, hypothesizing that measured T1blood would be the most suited for CBF quantification in children with sickle cell disease.

MATERIALS AND METHODS: Four approaches for T1blood 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 (T1blood-fixed); second, T1blood calculated from hematocrit measured in patients (T1blood-hematocrit); third, T1blood measured in vivo with a Look-Locker MR imaging sequence (T1blood-measured); and finally, a mean value from T1blood measured in this study in children with sickle cell disease (T1blood-sickle cell disease). Quantitative flow measurements acquired with phase-contrast MR imaging served as reference values for CBF.

RESULTS: T1blood-measured (1818 ± 107 ms) was higher than the literature recommended value of 1650 ms, was significantly lower than T1blood-hematocrit (2058 ± 123 ms, P < .001), and, most interesting, did not correlate with hematocrit measurements. Use of either T1blood-measured or T1blood-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 T1blood 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; T1blood = longitudinal relaxation time of blood.

In vivo T1 of blood measurements in children with sickle cell disease may improve cerebral blood flow quantification from arterial spin-labeling MRI. Quantitative CBF values are obtained by using an estimation of the longitudinal relaxation time of blood (T1blood). Because T1blood depends on hematocrit in healthy individuals, we investigated the importance of measuring T1blood in vivo with MR imaging versus calculating it from hematocrit or assuming an adult fixed value recommended by the literature, hypothesizing that measured T1blood would be the most suited for CBF quantification in children with sickle cell disease.

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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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Two healthy adults, with a stable Hct, a fixed T1blood value of 1650 ms is recommended for CBF quantification from pseudocontinuous ASL (pCASL) at 3T.13,14 T1blood is inversely correlated with Hct,10,13,13,19 and a linear relationship has been proposed in the literature permitting the calculation of T1blood 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, T1blood can be derived accordingly. However, recent studies suggest that T1blood may additionally differ in children with SCD.12,22,23

Owing to recent developments in MR imaging, direct measurements of the inversion recovery of T1blood 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 T1blood measurements are noninvasive, robust, and fast, making them preferable to calculating T1blood from blood samples. Our first hypothesis was that in vivo–measured T1blood 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 T1blood.12 We investigated the importance of measuring patient-specific differences in T1blood for the accuracy of ASL quantification in patients with SCD. We hypothesized that patient-specific T1blood values acquired in vivo would improve CBF quantification in SCD compared with CBF quantification with T1blood calculated from Hct or T1blood-fixed at 1650 ms.

The aim of this study was to determine which of the following 4 T1blood 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 T1blood of 1650 ms,14 2) T1blood calculated from Hct, 3) in vivo–measured T1blood, or 4) a fixed average SCD value from the mean T1blood 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 HbSβ0 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 T1blood-Hct values.

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, T1blood, 2D pseudocontinuous ASL, and 2D phase-contrast sequences.

The T1blood acquisition section was planned perpendicular to the posterior sagittal sinus16 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 × 1.5 mm; matrix, 240 × 240 mm; section thickness, 2 mm; TE/TR, 15/10,000 ms; T1t, 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, 7/4000 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 non-triggered 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.

Table 1: Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Demographic or Clinical Parameter</th>
<th>Mean and SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>39</td>
</tr>
<tr>
<td>Females (No. and % of total)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>Males (No. and % of total)</td>
<td>23 (59%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>Hemoglobin (g/d/L)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.4 ± 1.1</td>
</tr>
<tr>
<td>Hemoglobin F (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>Hemoglobin A2 (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.8 ± 1</td>
</tr>
<tr>
<td>Hemoglobin S (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>84 ± 5</td>
</tr>
<tr>
<td>Mean corpuscular volume (mL)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>82 ± 10</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (mmol/L)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>21 ± 0.6</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Normal range reference values: Hb = 10–16.
<sup>b</sup> HbF < 1%.
<sup>c</sup> HbA2 = 2–3.
<sup>d</sup> MCV = 75–95.
<sup>e</sup> MCHC = 19.0–22.5.
The T1blood parameter was adjusted for each patient as a function of the sum of least-squares fit. The sum of squared errors from fitting the T1blood-measured values to the model was used, as published in detail previously9,26 (except that the equilibrium magnetization of arterial blood was derived from the mean Hct, 23% ± 3%) [Pearson r = 0.02, P = .89; n = 39].

| Table 2: T1blood values and corresponding CBF values quantified from ASL* |
|------------------|------------------|------------------|
| T1blood Method | Value | ASL-CBF (mL/100 g/min) | P Value |
| T1blood fixed | 1650 ms | 114 ± 13 | <.05 |
| T1blood Hct | Calculated from patient’s hematocrit (variable) | 95 ± 10 | <.05 |
| T1blood measured | Measured with MR in vivo in patients with SCD (variable) | 106 ± 14 | NS |
| T1blood SCD | Mean of T1blood measured (1818 ms) | 105 ± 12 | NS |

Note: NS indicates not significant.

*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

T1blood. 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 (Nealer-Mead method; MathWorks, Natick, Massachusetts), with the parameters M0, Offset, and T1blood,17 and solved for T1blood:

1) \( M(nTI) = abs \left( M_0 \times \left[ 1 - 2 \times \exp \left( - \frac{\text{Offset} + T_1 - (nTI - 1) \times \Delta TI}{T_{1\text{blood}}} \right) \right] \right) \),

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, \( T_1 \) is 200 ms, and \( \Delta TI \) is the sampling interval (150 ms). The sum of squared errors of the final (optimal) iteration after solving the Nealer-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 previously25 by using a processing pipeline for the registration and quantification of the data. A 2-compartment quantification model was used, as published in detail previously9,26 (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 T1blood parameter was adjusted for each CBF quantification as follows: first, adult fixed T1blood of 1650 ms taken from literature15; second, patient-specific Hct-calculated T1blood values16; third, patient-specific in vivo–measured T1blood values; and finally an average T1blood value obtained from the mean of in vivo T1blood measurements in our patients with SCD. T1blood-Hct was calculated per patient according to the relationship proposed by Varela et al16 derived from venous blood in neonates:

2) \( T_{1\text{blood}} = \frac{1}{0.5 \times \text{Hct} + 0.37} \).

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 T1blood-measured and Hct. Repeated-measures ANOVA was used to test the statistical significance of the differences among the 5 CBF quantification methods: 1) CBF (T1blood-fixed at 1650 ms), 2) CBF (T1blood-Hct), 3) CBF (T1blood-measured in vivo), 4) CBF (T1blood-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 T1blood 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 T1blood

The mean Hct was 23% ± 3% for 39 children. The mean T1blood-measured value was 1818 ± 107 ms, which was significantly lower than mean T1blood-Hct values (2045 ± 69 ms; paired \( t \) test, \( P < .001 \)) but higher compared to the fixed adult value of 1650 ms. T1blood-measured was not significantly different between scanners (\( t \) test, \( P = .94 \)). Figure 1A 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 T1blood-measured values to the model is shown in On-line Fig 1. T1blood-measured values did not correlate...
with Hct values measured from blood samples ($r = 0.02, P = .89; \text{Fig 1B}$) 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 $T_{1\text{blood}}$-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. $T_{1\text{blood}}$-fixed overestimated CBF and $T_{1\text{blood}}$-Hct underestimated CBF, while the individual in vivo $T_{1\text{blood}}$-measured values and mean $T_{1\text{blood}}$-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 $T_{1\text{blood}}$ measured from 2 patients is shown in Fig 3.

### DISCUSSION

We demonstrate that in vivo–measured venous $T_{1\text{blood}}$ 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 $T_{1\text{blood}}$. CBF quantified with in vivo–measured $T_{1\text{blood}}$ provided better agreement with PC-MRI reference measurements than CBF quantified with fixed adult $T_{1\text{blood}}$ and Hct-derived $T_{1\text{blood}}$.

### $T_{1\text{blood}}$ and Hematocrit

Previous literature suggests that healthy children 6–18 years of age (assuming a stable Hct of 40%–45%) have $T_{1\text{blood}}$ values between 1680 and 1880 ms. In this study, in patients with a much lower Hct than healthy children, we measured $T_{1\text{blood}}$ values closer to the upper range of the literature-reported $T_{1\text{blood}}$ values. Yet, our $T_{1\text{blood}}$ values were lower than expected, considering the low Hct values obtained from our patients’ blood samples. It is unlikely that we underestimated $T_{1\text{blood}}$ due to sequence-related limitations because the Look-Locker $T_1$ technique has previously provided robust results in the same ROI. Reports of $T_{1\text{blood}}$ values ranging from 1500 to 2100 ms follow a linear relationship with Hct between 23% and 50%. 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
was too narrow in our patients (17%–32%). Abnormalities in SCD blood, other than low Hct, may account for the incongruity between $T_1^\text{blood}$ 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 $T_1^\text{blood}$ 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 $T_1^\text{blood}$ ameliorates the CBF quantification but Hct-corrected $T_1^\text{blood}$ does not opposes the use of Hct-corrected CBF quantification in SCD and, instead, advocates the use of measured $T_1^\text{blood}$. $T_1^\text{blood}$ measurements are advantageous over Hct-calculated $T_1^\text{blood}$ because they are faster (1 minute 20 seconds) and less invasive. In the absence of $T_1^\text{blood}$ 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 $T_1^\text{blood}$ measurement and the potentially inaccurate reference flow measurements from PCMR.

Whereas $T_1^\text{blood}$ measurements were acquired in venous blood, the quantification model requires arterial estimates. However, because we compared venous $T_1^\text{blood}$ measurements with $T_1^\text{blood}$ values derived from venous Hct, the potential mismatch would have been similar for both methods. Moreover, we demonstrate that the measured venous $T_1^\text{blood}$ 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 over-estimation due to partial volume effects36 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 $T_1^\text{blood}$ estimates can be a major confounder for quantitative perfusion assessment from ASL. Patient-specific, in vivo measured $T_1^\text{blood}$ measurements provided more accurate CBF values than $T_1^\text{blood}$ derived from Hct values. To avoid overestimation of CBF in SCD, we recommend the use of a fixed value of 1818 ms ($T_1^\text{blood}$-SCD) for CBF quantification from ASL if measured $T_1^\text{blood}$ values are not available.

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**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.
REFERENCES


