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

Sicklcell disease (SCD) is associated with a considerable risk of stroke,1 which is reduced by blood transfusion therapy2 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 SCD4,5; 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.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 SCD5,8,9 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 (T1blood) parameter accounts for the decay of the ASL signal with time, and

Received December 15, 2015; accepted after revision February 24, 2016.
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This work was funded by the Dutch NutsOhra Foundation, Amsterdam, the Netherlands (grant 1503-055).
Paper previously presented, in part, at: Annual Meeting of the International Society for Magnetic Resonance in Medicine Benelux, January 16, 2015, Ghent, Belgium. Please address correspondence to Lena Václavu, MSc, Department of Radiology, Z0-178, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands; e-mail: l.vaclavu@amc.uva.nl

Indicates article with supplemental on-line photo.
http://dx.doi.org/10.3174/ajnr.A4793

AJNR Am J Neuroradiol 37:1727–32 Sep 2016 www.ajnr.org 1727
inaccurate estimates of $T_{1\text{blood}}$ could result in over- or underestimation of CBF.\textsuperscript{10,12} For healthy adults, with a stable Hct, a fixed $T_{1\text{blood}}$ value of 1650 ms is recommended for CBF quantification from pseudocontinuous ASL (pCASL) at 3T.\textsuperscript{13,14} $T_{1\text{blood}}$ is inversely correlated with Hct,\textsuperscript{10,13,13-19} and a linear relationship has been proposed in the literature permitting the calculation of $T_{1\text{blood}}$ from measured Hct values.\textsuperscript{12,13,16} While Hct ranges from 38% to 45% in healthy children,\textsuperscript{20} it is as low as 18%–30% in children with SCD.\textsuperscript{21} Hence, if measured Hct values are available, $T_{1\text{blood}}$ can be derived accordingly. However, recent studies suggest that $T_{1\text{blood}}$ may additionally differ in children with SCD.\textsuperscript{12,22,23}

Owing to recent developments in MR imaging, direct measurements of the inversion recovery of $T_{1\text{blood}}$ are now possible by combining a global inversion pulse and a subsequent section-selective Look-Locker readout in the sagittal sinus.\textsuperscript{16,17} Patient-specific, in vivo $T_{1\text{blood}}$ measurements are noninvasive, robust, and fast, making them preferable to calculating $T_{1\text{blood}}$ from blood samples. Our first hypothesis was that in vivo–measured $T_{1\text{blood}}$ 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 $T_{1\text{blood}}$.\textsuperscript{12} We investigated the importance of measuring patient-specific differences in $T_{1\text{blood}}$ for the accuracy of ASL quantification in patients with SCD. We hypothesized that patient-specific $T_{1\text{blood}}$ values acquired in vivo would improve CBF quantification in SCD compared with CBF quantification with $T_{1\text{blood}}$ calculated from Hct or $T_{1\text{blood}}$-fixed at 1650 ms.

The aim of this study was to determine which of the following 4 $T_{1\text{blood}}$ 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 $T_{1\text{blood}}$ of 1650 ms,\textsuperscript{14} 2) $T_{1\text{blood}}$ calculated from Hct, 3) in vivo–measured $T_{1\text{blood}}$, or 4) a fixed average SCD value from the mean $T_{1\text{blood}}$ 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.\textsuperscript{14} 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 $T_{1\text{blood}}$-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, 3D phase-contrast MR imaging (PC-MRI): 1) literature-recommended adult $T_{1\text{blood}}$ of 1650 ms,\textsuperscript{14} 2) $T_{1\text{blood}}$ calculated from Hct, 3) in vivo–measured $T_{1\text{blood}}$, or 4) a fixed average SCD value from the mean $T_{1\text{blood}}$ measured in vivo in this study.

| 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/dL)\textsuperscript{a} | 8.4 ± 11   |
| Hemoglobin F (%)\textsuperscript{b} | 10 ± 6     |
| Hemoglobin A2 (%)\textsuperscript{c} | 4.8 ± 1    |
| Hemoglobin S (%)\textsuperscript{c} | 84 ± 5     |
| Mean corpuscular volume (mL)\textsuperscript{d} | 82 ± 10    |
| Mean corpuscular hemoglobin concentration (mmol/L)\textsuperscript{e} | 21 ± 0.6  |

\textsuperscript{a}Normal range reference values: Hb = 10–16.
\textsuperscript{b}Hbf < 1%.
\textsuperscript{c}HbA2 = 2–3.
\textsuperscript{d}MCH = 75–95.
\textsuperscript{e}MCHC = 19.0–22.5.

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, 1 minute 20 seconds).

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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.
and solved for $T_{1\text{blood}}$ by using a processing pipeline for the registration and label-magnetization, "Offset" accounts for imperfect inversion, $T_1$ is 200 ms, and $\Delta T$ 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 previously, 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 (except that the equilibrium magnetization of arterial blood was derived from the $M_0$ of CSF multiplied by the blood-water partition coefficient, and labeling efficiency was 0.7). The $T_{1\text{blood}}$ parameter was adjusted for each CBF quantification as follows: first, adult fixed $T_{1\text{blood}}$ of 1650 ms taken from literature; second, patient-specific Hct-calculated $T_{1\text{blood}}$ values; third, patient-specific in vivo–measured $T_{1\text{blood}}$ values; and finally an average $T_{1\text{blood}}$ value obtained from the mean of in vivo $T_{1\text{blood}}$ measurements in our patients with SCD. $T_{1\text{blood}}$-Hct was calculated per patient according to the relationship proposed by Varela et al, derived from venous blood in neonates:

$$T_{1\text{blood}} = \frac{1}{0.5 \times \text{Hct} + 0.37}.$$
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 \((t\text{-test}, P = .37)\).

**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 with limits of agreement \((\text{dotted lines above and below})\) \((n = 33)\).

**FIG 2.** Linear regression and Bland-Altman plots between CBF values measured with PC-MRI and ASL, which was quantified by using 4 different \(T1_{\text{blood}}\) values: a fixed literature value of 1650 ms \((\text{CBF } T1_{\text{blood-fixed}})\) \((A \& B)\); \(T1_{\text{blood}}\) calculated from hematocrit \((\text{CBF } T1_{\text{blood-Hct}})\); \(T1 = 0.5\text{Hct} + 0.37\) \((C \& D)\); in vivo–measured \(T1_{\text{blood}}\) \((\text{CBF } T1_{\text{blood-measured}})\) \((E \& F)\); and a fixed SCD value obtained from the mean of the in vivo–measured \(T1_{\text{blood}}\) \((\text{CBF } T1_{\text{blood-SCD}})\) \((G \& H)\). The left panel shows linear regressions \((\text{solid line})\), 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 \((\text{dotted lines above and below})\) \((n = 33)\).

are shown in the left panel of Fig 2 and reveal slopes significantly different from zero for all CBF quantifications except for the \(T1_{\text{blood-Hct}}\) 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. \(T1_{\text{blood-fixed}}\) overestimated CBF and \(T1_{\text{blood-Hct}}\) underestimated CBF, while the individual in vivo \(T1_{\text{blood-measured}}\) provided 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 \(T1_{\text{blood-measured}}\) measured from 2 patients is shown in Fig 3.

**DISCUSSION**

We demonstrate that in vivo–measured venous \(T1_{\text{blood}}\) 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 \(T1_{\text{blood-measured}}\) CBF quantified with in vivo–measured \(T1_{\text{blood}}\) provided better agreement with PC-MRI reference measurements than CBF quantified with fixed adult \(T1_{\text{blood}}\) and Hct-derived \(T1_{\text{blood}}\).

**T1_{\text{blood}} and Hematocrit**

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

Reports of \(T1_{\text{blood}}\) 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
was too narrow in our patients (17%–32%). Abnormalities in SCD blood, other than low Hct, may account for the incongruity between T1blood 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.1,30-34 Furthermore, red blood cells in SCD exhibit different membrane properties and viscosity, which may have reduced T1blood 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 T1blood ameliorates the CBF quantification but Hct-calculated T1blood does not opposes the use of Hct-corrected CBF quantification in SCD and, instead, advocates the use of measured T1blood. T1blood measurements are advantageous over Hct-calculated T1blood because they are faster (1 minute 20 seconds) and less invasive. In the absence of T1blood 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 T1blood measurement and the potentially inaccurate reference flow measurements from PCMR.

Whereas T1blood measurements were acquired in venous blood, the quantification model requires arterial estimates. However, because we compared venous T1blood measurements with T1blood values derived from venous Hct, the potential mismatch would have been similar for both methods. Moreover, we demonstrate that the measured venous T1blood 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 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 T1blood estimates can be a major confounder for quantitative perfusion assessment from ASL. Patient-specific, in vivo–measured T1blood measurements provided more accurate CBF values than T1blood derived from Hct values. To avoid overestimation of CBF in SCD, we recommend the use of a fixed value of 1818 ms (T1blood-SCD) for CBF quantification from ASL in SCD if measured T1blood values are not available.

**ACKNOWLEDGMENTS**

The authors thank the participants and the medical and technical staff who helped with recruitment, scanning, and blood measurements.

Disclosures: Lena Václavů—RELATED: Grant: Fonds NutsOhra (grant from Dutch Sickle Cell Research Foundation).* Dennis F.R. Heijtel—UNRELATED: Employment: Philips Healthcare [currently employed]. Matthias J.P. van Osch—UNRELATED: Employment: Philips Healthcare. Patients (planned, pending or issued): joint patent with Philips Healthcare* and a joint patent with the Florey Institute of Neuroscience and Mental Health [Melbourne, Australia] and Lund University [Sweden]* both pending; Other: research support by Philips Healthcare.* Charles B.L.M. Majoe—UNRELATED: Payment for Lectures (including service on Speakers Bureau): Stryker.* John C. Wood—UNRELATED: Consultancy: BioMed Informatics, ApoPharma, biss Pharmaeuticals, Pfizer, Celgene, WorldCare Clinical; Grants/Grants Pending: National Institutes of Health [U01HL117718–01 from the National Heart, Lung, and Blood Institute].* National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases [R01DK09715–01A1].* Comments: Work-in-Kind—Philips provided technical expertise, pulse sequences, and engineering staff and we have tested new MRI techniques, product feedback, and academic productivity (abstracts and papers).* Money paid to the institution.
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