Published in final edited form as:

J Neuroradiol. 2019 February ; 46(1): 29–35. doi:10.1016/j.neurad.2018.03.002.

Effect of Blood T1 Estimation Strategy on Arterial Spin Labeled Cerebral Blood Flow Quantification in Children and Young Adults with Kidney Disease

Hua-Shan Liu, PhD,

School of Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan; Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; International Ph.D. Program in Biomedical Engineering & Graduate Institute of Biomedical Optomechatronics, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan; Radiogenomic Research Center, Taipei Medical University Hospital, Taipei, Taiwan

Abbas F. Jawad, PhD,

Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Nina Laney, BA,

Division of Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Erum A. Hartung, MD,

Division of Nephrology, Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Susan L. Furth, MD PhD, and

Division of Nephrology, Departments of Pediatrics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania; Division of Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

John A. Detre, MD

Departments of Neurology and Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Abstract

Purpose—To compare blood T1 estimation approaches used for quantifying cerebral blood flow (CBF) with arterial spin labeled (ASL) perfusion MRI in a developmental cohort of chronic kidney disease (CKD) patients with anemia and a control group.

Corresponding author: John A. Detre, MD, Departments of Neurology and Radiology, Perelman School of Medicine at the University of Pennsylvania, 3W Gates Pavillion, 3400 Spruce Street, Philadelphia, PA 19104 USA. detre@mail.med.upenn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure

All of the authors declared no competing interests.

Methods—61 patients with CKD and 47 age-matched control subjects were studied. Blood T1 approaches included: (1) a fixed value, (2) estimation based on measured hematocrit (Hct), and (3) estimation based on Age+Sex using a published formula. Resulting T1 and CBF values were compared along with group, age and sex effects.

Results—Highly significant group differences in CBF using fixed blood T1 were reduced when Hct-corrected blood T1 was used, and were eliminated entirely when using the Age+Sex estimated approach. In the control cohort, fixed T1 method showed the strongest correlations of CBF with age and sex. Hct-corrected T1 preserved a significant correlation between CBF and age and sex, while Age+Sex estimated T1 produced a poor fit of CBF with age and sex.

Conclusions—Blood T1 estimation method can confound the interpretation of CBF changes measured using ASL MRI in patients with CKD. Blood T1 should ideally be corrected for hematocrit effects in clinical populations with anemia.

Keywords

arterial spin labeling; T1 correction; cerebral blood flow; anemia; chronic kidney disease

Introduction

Arterial spin labeling (ASL) employs radiofrequency and magnetic field gradient pulses to magnetically label the spins of the flowing arterial blood allowing tissue perfusion to be quantified without using extrinsic contrast agents (1). However, various technical factors need to be considered for accurate implementation of this technique in clinical applications (2, 3). High field MRI can increase the signal-to-noise ratio (SNR) and the proton labeling time due to the increased T1 of labeled blood (4). The post-labeling delay (PLD) or TI also needs to be sufficiently short to avoid excess relaxation of the labeled protons and be longer than arterial transit time (ATT) to give enough time for the labeled protons to reach the capillaries and suppress most of the intravascular signal in ASL. The range of ATT depends on age, so the PLD should be adjusted accordingly in pediatric applications (5).

One key parameter linking ASL signal changes to quantitative perfusion is the longitudinal relaxation time (T1) of arterial blood, which is used to correct for signal decay of the magnetically labeled blood water between labeling and imaging. In routine clinical settings of ASL quantification, blood T1 is often assumed to be a fixed value(6, 7) or sometimes modeled value based on age and sex(8). An alternative strategy is to calculate blood T1 based on measured hematocrit(6) since blood T1 depends on hematocrit(9, 10). This may be particularly important for studies involving patients with anemia since reduced Hct can prolong the T1 of arterial blood(9).

Chronic kidney disease (CKD) is characterized by a progressive loss in kidney function over a period of months or years and results in a number of systemic complications including anemia due to a decrease in erythropoietin production(11). It affects 12% of US adults and is associated with increased risks of stroke and dementia(12, 13). Previous studies have suggested a link between impairment in kidney function and cognitive impairment mediated through vascular mechanisms(12). Given the high incidence of cardiovascular disease in

CKD and the associations between CKD and neurological dysfunction(14–16), further characterization of cerebrovascular function in CKD is highly relevant. The entirely noninvasive nature of ASL MRI without requirement for contrast administration also makes it particularly well suited to study the population with kidney dysfunction such as CKD in whom gadolinium contrast is contraindicated(17, 18). However, existing data on CBF in CKD are limited, particularly for pediatric CKD. Examining cerebrovascular function in a pediatric population with CKD provides the potential to dissociate CKD effects from those of associated chronic hypertensive vasculopathy which is often a consequence of age-related disorders. A few recent studies of adult CKD have shown increased CBF in CKD(13, 19), however, Hct was not assessed and corrected in their ASL CBF measurements, and especially prominent correlation of CBF with Hct was noted(19).

In the present study, we evaluated and compared pseudocontinuous ASL CBF measurements in a cohort of children and young adults with CKD and controls modeled using three most commonly used approaches for blood T1; a fixed blood T1 value of 1664 msec derived from the literature(6, 7), a Hct-corrected value based on a concurrently-acquired complete blood count(6), and an estimated value based on a published formula that includes age and sex(8). To further assess the validity of derived CBF values using these approaches, we also tested for expected age and sex effects in the control cohort.

Methods

Participants

Sixty-one patients with any stage of CKD II to V (defined as estimated glomerular filtration rate, eGFR <90 ml/min/1.73m² using modified Schwartz formula, on dialysis, and post-transplant) and 47 age-matched control subjects were included in this study (Table 1 and supplementary materials). Participants in the typically developing control group had no reported personal history of CKD, nor any reported history of other neurological or psychiatric conditions. Laboratory data of complete blood count were collected from each participant on the same day that ASL MRI was carried out. Informed consent was obtained from all participants and their caregivers with approval from the ethics committee of the Children's Hospital of Philadelphia.

Data acquisition

ASL data—MRI data were acquired on a 3-T whole-body Siemens Verio scanner (Erlangen, Germany) with an 8-channel receive-only head coil and body coil transmission. High-resolution structural MRI (MPRAGE sequence, 0.9×0.8×0.8 mm³, TR/TE=2000/3.3 ms) data were collected for each participant. Resting CBF measurements were acquired using pseudocontinuous ASL(20) (see supplementary materials).

Data processing and analysis

ASL CBF data—MRI data were processed using Statistical Parametric Mapping (SPM8) and customized MATLAB scripts (The Mathworks Inc., Natick, MA). CBF maps were calculated using a modified perfusion data processing toolbox, ASLtbx (21). Global CBF

values of whole brain (WB), gray matter (GM), and white matter (WM) areas were obtained from non-normalized segmented images.

Blood T1 values were estimated using three different approaches: (1) a fixed value of 1664 msec for all subjects at a typical human Hct of 0.42 as reported(6, 7), (2) Hct-based using the equation derived by Lu et al(6); $T1 = 1 / (0.52 * Hct + 0.38)$ based on a Hct measurement performed at the time of the MRI scan, and (3) Age+Sex based using the method derived by Wu et al(8); $(T1 = 2115.6 - 21.5 * age - 73.3 * sex)$, where sex=1 for males and 0 for females).

Statistical analysis

Demographics and clinical measurements collected from the CKD and control subjects were compared using generalized linear models (GLM) with group, sex and group $\times$ sex as the independent variables. The Chi-squared test or the Fisher's exact test was used for comparing categorical variables. Linear mixed-effects regression modeling was used to compare T1 and CBF values from the three methods of calculation. The SAS Proc Mixed procedure was employed with T1 and CBF values as the dependent variable, blood T1 estimation method as the independent variables and the three different methods as the within-subjects factor. Study groups (CKD vs control) and sex (male vs female) are the between subject independent variables and considered as a fixed effect, while the intercepts were defined as a random effect. Two and three interactions terms between calculation method, group, and sex were added as independent variables. Prior to conducting statistical testing, each outcome measure was carefully examined to identify outliers and to determine whether the assumptions needed for parametric testing were met. An alpha level of 0.05 was set as our threshold for significant values for these comparisons. The SAS software version 9.4 and SPSS software version 20.0 were used to conduct the analyses.

Univariate associations between measurements of Hct, age and sex were analyzed using Spearman correlation in the control cohort. To evaluate the effects of age and sex on CBF using three different T1 methods, separate multiple regression analyses were conducted to determine whether calculated CBF was associated with age and sex in the control cohort. CBF was treated as the dependent variable and age and sex as the independent variables in the regression analysis. As age and sex effects are known modulators of CBF and Hct in normal brain development (22–24), an observation of significant correlations between age and sex supports the validity of derived CBF values. However, children with CKD are known to show altered developmental trajectories (25). Accordingly, Spearman correlation and multiple regression analyses testing for age effects on CBF was only carried out in the control cohort. A multivariable linear regression was also carried out in control subjects to derive a model of blood T1 change as a function of age and sex using Hct-corrected T1 as the dependent variable. T1 was treated as the dependent variable and age and sex as the independent variables (8).

Results

Table 1 summarizes demographic information on the study cohort. The CKD group included a significantly higher proportion of males than the control group (Fisher's exact test $P=0.0476$). No other demographic differences or interactions were observed. CKD patients

had significantly lower Hct as compared with control subjects (38.01 ± 4.98 vs 41.12 ± 4.12), ($F_{1, 104} = 14.41$, $P=0.0002$). Females also had significant lower Hct level than males (38.35 ± 4.33 vs 40.04 ± 5.10), ($F_{1, 104} = 7.54$, $P=0.0071$), but no significant group $\times$ sex interaction was seen for Hct ($F_{1, 104} = 1.15$, $P=0.2860$).

Table 2 shows the results of calculated blood T1 and CBF values for each subgroup obtained using the three different blood T1 estimation methods. On average, the Age+Sex based method generated higher estimated blood T1 values as compared with the fixed literature-based T1 and Hct-based method, and the Hct-based method generated higher blood T1 values as compared with the fixed T1 method (Table 2). Accordingly, the fixed T1 method generated higher CBF values than the Hct and Age+Sex based methods, and the Hct-based method generated higher CBF values than the Age+Sex-based method (Table 2).

Table 3 shows results from linear mixed-effects regression analyses comparing T1 and CBF values using three different T1 method. Estimated GM CBF showed significant effects of method, group, and interactions of method $\times$ group and method $\times$ sex (Table 3, $P<0.05$). The main effect of sex and the interaction terms of group $\times$ sex and method $\times$ group $\times$ sex were not significant (Table 3, $P>0.05$). For WM CBF, only method and the interaction of method $\times$ group were significant (Table 3, $P<0.05$). WB CBF showed significant effects of method, and significant interactions of method $\times$ group and method $\times$ sex (Table 3, $P<0.05$). This analysis also demonstrated that effects of group and sex on CBF are significantly different when different T1 approaches were used.

Use of a fixed T1 value without considering the effect of Hct produced the strongest group differences in GM and WB CBF between CKD and controls (Figure 1), but these differences represent both true CBF effects and Hct effects on ASL CBF quantification. Use of Hct-corrected T1 still showed significant group differences in GM and WB CBF (Figure 1). Age +Sex estimated T1 did not yield any significant group differences (Figure 1). In controls, females showed higher CBF values as compared with males using all of the T1 methods, though significant differences using fixed T1 (Figure 1 and Table 2) were no longer present using the Hct-based corrected T1 method (Figure 1) and the Age+Sex based T1 method (Figure 1). Sex differences in CBF were not present in CKD using any of the models (Figure 1).

There were strong correlations between Hct and age (Spearman correlation, $\rho=0.50$, $P<0.001$), and between Hct and sex (Spearman correlation, $\rho=0.38$, $P=0.01$) in our control subjects.

Table 4 shows regression results obtained in the control cohort for CBF with age and sex using the three different T1 methods. Similar to group effect findings, the fixed T1 method showed the strongest correlations of CBF with age and sex. However, use of Hct-corrected T1 still resulted in a significant correlation between CBF and age and sex. Use of Age+Sex estimated T1 produced a poor fit of CBF with age and sex with no significant correlations observed. In the control cohort, both age and sex showed a significant correlation with Hct derived blood T1 ($P=0.0015$ and $P=0.0050$, respectively). The fitted regression line was: $T1 = 1817 - 8.2 * \text{age} - 37.4 * \text{sex}$. ($F=11.1$, $P=0.0001$; Sex: male=1, female=0).

Discussion

In the present study, we evaluated three commonly used approaches in the clinic for estimating blood T1 for quantitative CBF modeling using ASL MRI data obtained from a cohort of children and young adults with CKD and controls. We observed significant differences in blood T1 depending on the approach used, leading to different findings for both sex and group differences in CBF. Highly significant group differences in CBF observed with method of fixed blood T1 were reduced when Hct-corrected blood T1 was used. Use of Hct-corrected T1 still showed significant group differences in GM and WB CBF. Increased CBF seen in CKD likely driven by rheological effects of anemia (26). Group differences in CBF were eliminated entirely when using the Age+Sex estimated approach, despite expected effects of anemia on CBF in CKD. Our findings highlight the importance of blood T1 in ASL CBF quantification, especially for patients such as CKD who have significant alterations in Hct. Hct-corrected blood T1 minimized spurious correlations of CBF with Hct while preserving expected correlations between CBF and Hct. Residual group effects of CKD on ASL CBF after Hct correction likely reflects true hyperperfusion rather than artifactual hyperperfusion due to T1 underestimation. The absence of sex differences in CBF in patients with CKD may reflect delayed sexual differentiation that is known to occur in children with CKD(25), or alternatively may be attributed to reduced sex differences in Hct, which has direct rheological effects on CBF(26).

A recent report on children with sickle cell disease (SCD) also compared CBF values derived using different blood T1 approaches(27), including an MRI method for measuring T1 in the sagittal sinus in vivo(28). They also found that CBF varied significantly with blood T1 approach, and recommended using either a disease-specific fixed value, or MRI measured blood T1 value. In that work, which did not include a control group, correlations with CBF derived from phase contrast MRI(29) were used to evaluate T1 estimation strategies. However, we recently reported that CBF from phase-contrast MRI is likely not an effective “gold standard” for calibration of ASL CBF(30). In addition, in the SCD study the MRI measured blood T1 did not correlate with Hct(27), as would be expected(10). The authors attributed the discrepant relationship between T1 and Hct to altered red cell membranes and viscosity changes particular to SCD. In contrast, Hct changes in CKD are due to a decrease in erythropoietin production(11). Unfortunately, our multimodal MRI protocol for CKD did not include either MRI measured blood T1 or phase contrast MRI, so we are unable to report on either the correlation between MRI measured blood T1 and Hct derived blood T1 or the correlations between our various T1 estimation methods and CBF derived from phase contrast MRI.

We included a control cohort to further assess the effects of age and sex on CBF as a means of comparing different T1 approaches as age and sex effects are known modulators of CBF(22, 23). Our control cohort demonstrated significant correlations between Hct and age, and between Hct and sex, though in the case of fixed T1 these correlations of CBF with age and sex likely reflected underlying correlations between Hct and both age and sex. Hct-corrected blood T1 method still resulted in a significant correlation of CBF with age while the Age+Sex blood T1 method (8) produced much poorer fits. Taken together, these results

suggest that Hct-corrected blood T1 provides a more optimized measure of true CBF effects in age and sex.

Data from our control cohort also provided an improved fit to the prior model of Wu et al(8) by showing significant effects of both age and sex on T1 values and an improved overall fit. However, modeling of sex as a fixed offset is probably not ideal because sex effects likely only occur after puberty(31). Nonetheless this model approximates the data reasonably well, and can be used for healthy developmental cohorts when concurrent Hct data are not available. A larger developmental cohort including more peripubertal subjects of both sexes would be needed to develop a more accurate model including effects of puberty and further studies should apply corrected CBF from T1 correction in a cohort of adults from different ages with CKD and controls. Estimation of blood T1 from individual Hct has been suggested by others as a good alternative while blood T1 sequences and their postprocessing tools are not readily available on most MR platforms (32).

In conclusion, our findings demonstrate that different T1 blood estimation methods in ASL technique can significantly alter apparent CBF changes in patients with CKD, and likely any populations with varying hematocrit. Our finding underscores the importance of accounting for Hct in ASL MRI quantification, since Hct changes are commonly seen in nearly all patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We want to thank the network of primary care clinicians, their patients and families for their contribution to this project and clinical research facilitated through the Pediatric Research Consortium (PeRC) at The Children's Hospital of Philadelphia. Please remember to ALSO cite the Institutional Clinical and Translational Science Award Research Center for publications that resulted from work at this Center: NIH/NCATS (National Center for Advancing Translational Sciences), Grant UL1TR000003.

Funding

The sources of support:

This project is funded, in part, under a Commonwealth Universal Research Enhancement grant with the Pennsylvania Department of Health, # SAP 4100054843. The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.

Study data were collected and managed using REDCap electronic data capture tools hosted at The Children's Hospital of Philadelphia. REDCap (Research Electronic Data Capture) (*Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.*) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The Clinical and Translational Research Center at the Children's Hospital of Philadelphia is supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grants UL1RR024134 and UL1TR000003. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

This work was also supported in part by the National Institutes of Health (grants MH080729 and EB015893).

Hua-Shan Liu was supported by Taipei Medical University (grant TMU103-AE1-B29), Taipei Medical University Hospital (grants 105TMU-TMUH-05 and 106TMU-TMUH-21) and Ministry of Science and Technology, R.O.C (grants MOST105-2218-E-038-003-MY2 and MOST106-2221-E-038-004-MY2).

References

1. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. *Magn Reson Med*. 1992; 23(1): 37–45. [PubMed: 1734182]
2. Kumar S, Nagesh CP, Thomas B, Radhakrishnan A, Menon RN, Kesavadas C. Arterial spin labeling hyperperfusion in Rasmussen's encephalitis: Is it due to focal brain inflammation or a postictal phenomenon? *J Neuroradiol*. 2017
3. Pavilla A, Arrigo A, Colombani S, Mejdoubi M. Absolute and regional cerebral perfusion assessment feasibility in head-down position with arterial spin-labeling magnetic resonance. A preliminary report on healthy subjects. *J Neuroradiol*. 2016; 43(6):392–7. [PubMed: 27126633]
4. Wang J, Alsop DC, Li L, et al. Comparison of quantitative perfusion imaging using arterial spin labeling at 1.5 and 4.0 Tesla. *Magn Reson Med*. 2002; 48(2):242–54. [PubMed: 12210932]
5. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med*. 2015; 73(1):102–16. [PubMed: 24715426]
6. Lu H, Clingman C, Golay X, van Zijl PC. Determining the longitudinal relaxation time (T1) of blood at 3.0 Tesla. *Magn Reson Med*. 2004; 52(3):679–82. [PubMed: 15334591]
7. Chen Y, Wang DJ, Detre JA. Test-retest reliability of arterial spin labeling with common labeling strategies. *J Magn Reson Imaging*. 2011 Apr; 33(4):940–9. [PubMed: 21448961]
8. Wu WC, Jain V, Li C, et al. In vivo venous blood T1 measurement using inversion recovery true-FISP in children and adults. *Magn Reson Med*. 2010; 64(4):1140–7. [PubMed: 20564586]
9. Gevers S, Nederveen AJ, Fijnvandraat K, et al. Arterial spin labeling measurement of cerebral perfusion in children with sickle cell disease. *J Magn Reson Imaging*. 2012; 35(4):779–87. [PubMed: 22095695]
10. Silvennoinen MJ, Kettunen MI, Kauppinen RA. Effects of hematocrit and oxygen saturation level on blood spin-lattice relaxation. *Magn Reson Med*. 2003; 49(3):568–71. [PubMed: 12594761]
11. Kuwabara Y, Sasaki M, Hirakata H, et al. Cerebral blood flow and vasodilatory capacity in anemia secondary to chronic renal failure. *Kidney Int*. 2002; 61(2):564–9. [PubMed: 11849397]
12. Sedaghat S, Vernooij MW, Loehrer E, et al. Kidney Function and Cerebral Blood Flow: The Rotterdam Study. *J Am Soc Nephrol*. 2016; 27(3):715–21. [PubMed: 26251352]
13. Tamura MK, Pajewski NM, Bryan RN, et al. Chronic kidney disease, cerebral blood flow, and white matter volume in hypertensive adults. *Neurology*. 2016; 86(13):1208–16. [PubMed: 26920359]
14. Yahalom G, Schwartz R, Schwammenthal Y, et al. Chronic kidney disease and clinical outcome in patients with acute stroke. *Stroke*. 2009; 40(4):1296–303. [PubMed: 19182072]
15. Moodalail DG, Reiser KA, Detre JA, et al. Systematic review of structural and functional neuroimaging findings in children and adults with CKD. *Clin J Am Soc Nephrol*. 2013; 8(8): 1429–48. [PubMed: 23723341]
16. Drew DA, Weiner DE. Cognitive impairment in chronic kidney disease: keep vascular disease in mind. *Kidney Int*. 2014; 85(3):505–7. [PubMed: 24583984]
17. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006; 21(4):1104–8. [PubMed: 16431890]
18. High WA, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol*. 2007; 56(1):21–6. [PubMed: 17097388]

19. Jiang XL, Wen JQ, Zhang LJ, et al. Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: an arterial-spin labeling MR imaging. *Metab Brain Dis*. 2016; 31(4):929–36. [PubMed: 27167984]
20. Wu WC, Fernández-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. *Magn Reson Med*. 2007; 58(5):1020–7. [PubMed: 17969096]
21. Wang Z, Aguirre GK, Rao H, et al. Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx. *Magn Reson Imaging*. 2008; 26(2):261–9. [PubMed: 17826940]
22. Rodriguez G, Warkentin S, Risberg J, Rosadini G. Sex differences in regional cerebral blood flow. *J Cereb Blood Flow Metab*. 1988; 8(6):783–9. [PubMed: 3192645]
23. Leenders KL, Perani D, Lammertsma AA, et al. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain*. 1990; 113(Pt 1):27–47. [PubMed: 2302536]
24. Mählkecht U, Kaiser S. Age-related changes in peripheral blood counts in humans. *Exp Ther Med*. 2010; 1(6):1019–25. [PubMed: 22993635]
25. Salas P, Pinto V, Rodriguez J, Zambrano MJ, Mericq V. Growth retardation in children with kidney disease. *Int J Endocrinol*. 2013:970946. [PubMed: 24187550]
26. Hudak ML, Koehler RC, Rosenberg AA, Traystman RJ, Jones MDJ. Effect of hematocrit on cerebral blood flow. *Am J Physiol*. 1986; 251(1 Pt 2):H63–70. [PubMed: 3728699]
27. Václav L, van der Land V, Heijtel DF, et al. In Vivo T1 of Blood Measurements in Children with Sick Cell Disease Improve Cerebral Blood Flow Quantification from Arterial Spin-Labeling MRI. *AJNR Am J Neuroradiol*. 2016; 37(9):1727–32. [PubMed: 27231223]
28. Varela M, Hajnal JV, Petersen ET, Golay X, Merchant N, Larkman DJ. A method for rapid in vivo measurement of blood T1. *NMR Biomed*. 2011; 24(1):80–8. [PubMed: 20669148]
29. Aslan S, Xu F, Wang PL, et al. Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. *Magn Reson Med*. 2010; 63(3):765–71. [PubMed: 20187183]
30. Dolui S, Wang Z, Wang DJ, et al. Comparison of non-invasive MRI measurements of cerebral blood flow in a large multisite cohort. *J Cereb Blood Flow Metab*. 2016; 36(7):1244–56. [PubMed: 27142868]
31. Giedd JN, Clasen LS, Lenroot R, et al. Puberty-related influences on brain development. *Mol Cell Endocrinol*. 2006; 254–255:154–62.
32. De Vis JB, Hendrikse J, Groenendaal F, et al. Impact of neonate haematocrit variability on the longitudinal relaxation time of blood: Implications for arterial spin labelling MRI. *Neuroimage Clin*. 2014; 4:517–25. [PubMed: 24818078]

Figure 1. CBF measurements using three different T1 methods (fixed T1, Hct based, and Age+Sex based) in each subgroup (males and females in CKD, and males and females in controls). A. gray matter (GM), B. white matter (WM) and C. whole brain (WB) areas. $*P<0.05$

Table 1

Subject age and hematocrit mean (SD) by groups and sex.

Group (n)	Sex (n, %)	Age	HCT (%)
CKD (61)	Male (42, 69%)	14.54 (2.70)	38.49 (4.88)
	Female (19, 31%)	14.80 (2.03)	36.97 (5.19)
Control (47)	Male (23, 48.9%)	14.65 (2.31)	42.88 (4.28)
	Female (24, 51.1%)	14.08 (2.98)	39.43 (3.21)

Table 2

Calculated CBF and T1 values using three different blood T1 estimation models.

Method	Group	GM CBF, ml/100g/min			WM CBF, ml/100g/min			WB CBF, ml/100g/min			T1, msec		
		male	female	male+ female	male	female	male+ female	male	female	male+ female	male	female	male+ female
Fixed T1	CKD	77.03 ± 14.56	77.16 ± 10.50	77.07 ± 13.34	34.34 ± 6.53	34.59 ± 5.61	34.42 ± 6.21	64.98 ± 11.68	65.77 ± 9.06	65.22 ± 10.86	1664 ± 0	1664 ± 0	1664 ± 0
	Control	65.28 ± 10.03	72.39 ± 10.81	68.91 ± 10.93	30.64 ± 4.34	33.64 ± 6.06	32.17 ± 5.44	55.61 ± 8.21	61.76 ± 8.64	58.75 ± 8.90	1664 ± 0	1664 ± 0	1664 ± 0
HCT based T1 correction	CKD	73.05 ± 11.88	71.20 ± 7.23	72.47 ± 10.63	32.21 ± 5.23	31.56 ± 3.77	32.00 ± 4.80	61.73 ± 9.48	60.81 ± 6.43	61.44 ± 8.61	1727 ± 79	1751 ± 85	1735 ± 82
	Control	65.47 ± 8.96	69.40 ± 9.07	67.48 ± 9.14	30.70 ± 3.58	32.06 ± 5.34	31.40 ± 4.57	55.77 ± 7.11	59.26 ± 7.14	57.55 ± 7.27	1660 ± 60	1711 ± 52	1686 ± 61
Age+Sex based T1 correction	CKD	70.25 ± 18.74	65.59 ± 18.79	68.80 ± 18.72	31.51 ± 8.59	28.41 ± 10.50	30.55 ± 9.25	59.33 ± 15.70	56.06 ± 16.02	58.31 ± 15.74	1729 ± 58	1797 ± 43	1751 ± 62
	Control	62.65 ± 8.87	66.42 ± 9.77	64.57 ± 9.43	29.32 ± 3.85	30.58 ± 5.24	29.96 ± 4.61	53.41 ± 7.17	56.76 ± 7.76	55.12 ± 7.58	1727 ± 49	1813 ± 64	1771 ± 72

GM: gray matter, WM: white matter, WB: whole brain.

Table 3

Results of linear mixed-effects regression comparing T1 and CBF values obtained using three different blood T1 estimation methods.

	T1		GM CBF		WM CBF		WB CBF	
	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value
Method	119.33	<.0001	51.74	<.0001	1778.05	<.0001	709.80	<.0001
Group	4.78	0.0299	7.62	0.0063	3.80	0.0527	2.98	0.0857
Sex	27.85	<.0001	0.80	0.3728	0.94	0.3341	0.23	0.6313
Method × Group	12.25	<.0001	16.27	<.0001	4.88	0.0085	6.85	0.0013
Method × Sex	16.55	<.0001	8.46	0.0003	0.79	0.4563	3.23	0.0417
Group × Sex	1.04	0.3081	2.11	0.1480	1.84	0.1761	2.29	0.1318
Method × Group × Sex	0.68	0.5640	1.01	0.3871	1.08	0.3606	0.89	0.4464

GM: gray matter, WM: white matter, WB: whole brain.

Table 4

Statistical results from multiple regression analyses of age and sex effects on CBF values in control cohort using three different T1 methods.

		fitted regression model sex: male=1, female=0	P-value for age	P-value for sex
Fixed T1	GM	CBF = 95.21–1.68 age –5.25 sex (F=8.42, P < 0.001)	0.002	0.05
	WM	CBF = 44.92–0.83 age –2.12 sex (F=6.86, P = 0.003)	0.003	0.13
	WB	CBF = 83.35–1.58 age –4.53 sex (F=12.05, P < 0.001)	P < 0.001	0.03
HCT based T1 correction	GM	CBF = 85.22–1.16 age –2.69 sex (F=3.99, P = 0.03)	0.02	0.28
	WM	CBF = 39.56–0.54 age –0.91 sex (F=2.84, P = 0.07)	0.03	0.49
	WB	CBF = 74.88–1.14 age –2.39 sex (F=6.49, P = 0.003)	0.002	0.21
Age+Sex based T1 correction	GM	CBF = 77.46–0.86 age –2.28 sex (F=2.23, P = 0.12)	0.08	0.36
	WM	CBF = 35.49–0.38 age –0.66 sex (F=1.40, P = 0.26)	0.13	0.61
	WB	CBF = 68.36–0.88 age –2.03 sex (F=3.72, P = 0.03)	0.02	0.30

GM: gray matter, WM: white matter, WB: whole brain.