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Original Article

Effect of blood *T*1 estimation strategy on arterial spin labeled cerebral blood flow quantification in children and young adults with kidney disease

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ABSTRACT

Purpose. – To compare blood *T*1 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.
Methods. – 61 patients with CKD and 47 age-matched control subjects were studied. Blood *T*1 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 *T*1 and CBF values were compared along with group, age and sex effects.
Results. – Highly significant group differences in CBF using fixed blood *T*1 were reduced when Hct-corrected blood *T*1 was used, and were eliminated entirely when using the Age + Sex estimated approach. In the control cohort, fixed *T*1 method showed the strongest correlations of CBF with age and sex. Hct-corrected *T*1 preserved a significant correlation between CBF and age and sex, while Age + Sex estimated *T*1 produced a poor fit of CBF with age and sex.
Conclusions. – Blood *T*1 estimation method can confound the interpretation of CBF changes measured using ASL MRI in patients with CKD. Blood *T*1 should ideally be corrected for hematocrit effects in clinical populations with anemia.

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 *T*1 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].

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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 ms 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–V (defined as estimated glomerular filtration rate, eGFR < 90 ml/min/1.73 m^2 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.

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)

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 mm × 0.8 mm × 0.8 mm, 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 ms 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]; $T1 = 1/(0.52^{*}\text{Hct} + 0.38)$ 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]; ($T1 = 2115.6 - 21.5^{*}\text{age} - 73.3^{*}\text{sex}$, 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 × 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 of CBF with 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 were 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 × 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 $T1$ methods. Estimated GM CBF showed significant effects of method, group, and interactions of method × group and method × sex (Table 3, $P < 0.05$). The main effect of sex and the interaction terms of group × sex and method × group × sex were not significant (Table 3, $P > 0.05$). For WM CBF, only method and the interaction of method × group were significant (Table 3, $P < 0.05$). WB CBF showed significant effects of method, and significant interactions of method × group and method × 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 (Fig. 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 (Fig. 1). Age + Sex estimated $T1$ did not yield any significant group differences (Fig. 1). In controls, females showed higher CBF values as compared with males using all of the $T1$ methods, though significant differences using fixed $T1$ (Fig. 1 and Table 2) were no longer present using the Hct-based corrected $T1$ method (Fig. 1) and the Age + Sex based $T1$ method (Fig. 1). Sex differences in CBF were not present in CKD using any of the models (Fig. 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 2
Calculated CBF and $T1$ values using three different blood $T1$ estimation models.

Method	Group	GM CBF, ml/100 g/min			WM CBF, ml/100 g/min			WB CBF, ml/100 g/min			$T1$, ms		
		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.

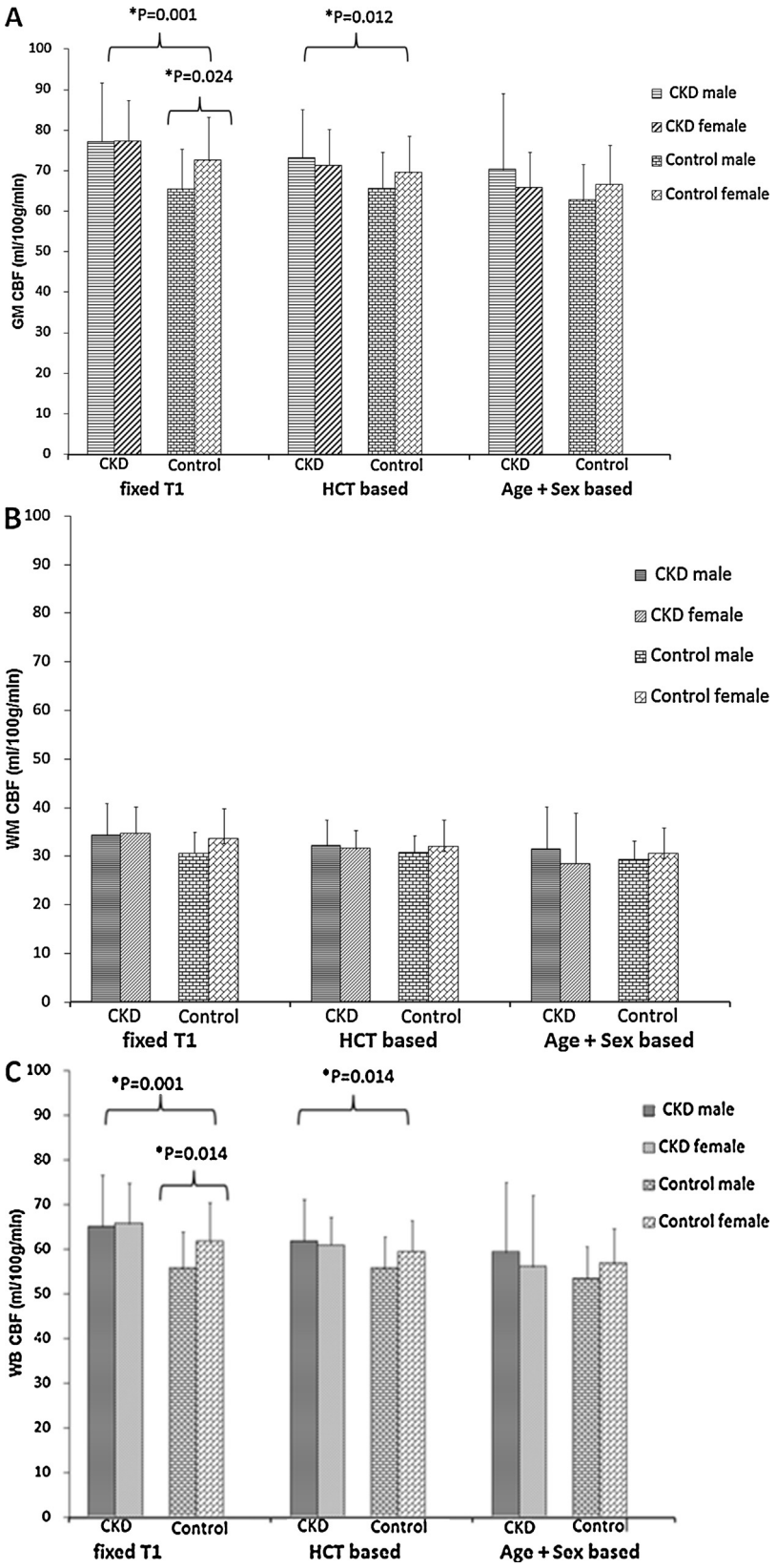

Fig. 1. CBF measurements using three different *T*1 methods (fixed *T*1, Hct based, and Age + Sex based) in each subgroup (males and females in CKD, and males and females in controls). A. gray matter (GM), B. white matter (WM) and C. whole brain (WB) areas. *$P < 0.05$.

Table 3
Results of linear mixed-effects regression comparing *T*1 and CBF values obtained using three different blood *T*1 estimation methods.

	*T*1		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 shows regression results obtained in the control cohort for CBF with age and sex using the three different *T*1 methods. Similar to group effect findings, the fixed *T*1 method showed the strongest correlations of CBF with age and sex. However, use of Hct-corrected *T*1 still resulted in a significant correlation between CBF and age and sex. Use of Age + Sex estimated *T*1 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 *T*1 ($P = 0.0015$ 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 *T*1 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 *T*1 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 *T*1 were reduced when Hct-corrected blood *T*1 was used. Use of Hct-corrected *T*1 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 *T*1 in ASL CBF quantification, especially for patients such as CKD who have significant alterations in Hct. Hct-corrected blood *T*1 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 *T*1 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 *T*1 approaches [27], including an MRI method for measuring *T*1 in the sagittal sinus in vivo [28]. They also found that CBF varied significantly with blood *T*1 approach, and recommended using either a disease-specific fixed value, or MRI measured blood *T*1 value. In that work, which did not include a control group, correlations with CBF derived from phase contrast MRI [29] were used to evaluate *T*1 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 *T*1 did not correlate with Hct [27], as would be expected [10]. The authors attributed the discrepant relationship between *T*1 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 *T*1 or phase contrast MRI, so we are unable to report on either the correlation between MRI measured blood *T*1 and Hct derived blood *T*1 or the correlations between our various *T*1 estimation methods and CBF derived from phase contrast MRI.

We included a control cohort to further access the effects of age and sex on CBF as a means of comparing different *T*1 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 *T*1 these correlations of CBF with age and sex likely reflected underlying correlations between Hct and both age and sex. Hct-corrected blood *T*1 method still resulted in a significant correlation of CBF with age while the Age + Sex blood *T*1 method [8] produced much poorer fits. Taken together, these results suggest that Hct-corrected blood *T*1 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 *T*1 values and an improved overall fit. However,

Table 4
Statistical results from multiple regression analyses of age and sex effects on CBF values in control cohort using three different *T*1 methods.

		Fitted regression model sex: male = 1, female = 0	*P*-value for age	*P*-value for sex
Fixed *T*1	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($F = 12.05$, $P < 0.001$)	<0.001	0.03
HCT based *T*1 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 *T*1 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.

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 *T*1 correction in a cohort of adults from different ages with CKD and controls. Estimation of blood *T*1 from individual Hct has been suggested by others as a good alternative while blood *T*1 sequences and their postprocessing tools are not readily available on most MR platforms [32].

In conclusion, our findings demonstrate that different *T*1 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.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurad.2018.03.002.

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