



Evaluation of Renal Blood Flow in Chronic Kidney Disease Using Arterial Spin Labeling Perfusion Magnetic Resonance Imaging

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Introduction: Chronic kidney disease (CKD) is known to be associated with reduced renal blood flow. However, data in humans are limited to date.

Methods: In this study, noninvasive arterial spin labeling magnetic resonance imaging data were acquired in 33 patients with diabetes and stage 3 CKD as well as in 30 healthy controls.

Results: A significantly lower renal blood flow in both the cortex (108.4 ± 36.4 vs. 207.3 ± 41.8 ; $P < 0.001$, $d = 2.52$) and medulla (23.2 ± 8.9 vs. 42.6 ± 15.8 ; $P < 0.001$, $d = 1.5$) was observed. Both cortical ($\rho = 0.67$, $P < 0.001$) and medullary ($\rho = 0.62$, $P < 0.001$) blood flow were correlated with estimated glomerular filtration rate, and cortical blood flow was found to be confounded by age and body mass index. However, in a subset of subjects who were matched for age and body mass index ($n = 6$), the differences between CKD patients and control subjects remained significant in both the cortex (107.4 ± 42.8 vs. 187.51 ± 20.44 ; $P = 0.002$) and medulla (15.43 ± 8.43 vs. 39.18 ± 11.13 ; $P = 0.002$). A threshold value to separate healthy controls and CKD patients was estimated to be a cortical blood flow of 142.9 and a medullary blood flow of 24.1.

Discussion: These results support the use of arterial spin labeling in the evaluation of renal blood flow in patients with a moderate level of CKD. Whether these measurements can identify patients at risk for progressive CKD requires further longitudinal follow-up.

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KEYWORDS: Arterial spin labeling; chronic kidney disease; eGFR; MRI; renal blood flow

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Recent advances in understanding the pathophysiology of chronic kidney disease (CKD) suggest that the pathogenic mechanisms causing progressive renal destruction converge on a common tubulo-interstitial pathway characterized by tubular atrophy and hypoxia, peritubular capillary injury, and interstitial fibrosis, finally leading to irreversible scarring.^{1,2} Prior studies have evaluated the use of blood oxygenation level-dependent and diffusion magnetic resonance imaging (MRI) to monitor differences in relative levels of hypoxia and interstitial fibrosis in patients with CKD.^{3,4} The key advantage of these 2 methods is that they are both endogenous contrast mechanisms and

require no administration of exogenous contrast media, which are contraindicated in subjects with compromised renal function.⁵ The ability to include an endogenous method to evaluate renal perfusion would be of great interest in developing a comprehensive functional protocol to understand the natural progression of CKD. Currently, there are not many data on renal blood flow or perfusion in patients with CKD.

Arterial spin labeling (ASL) MRI uses endogenous water as a tracer and is widely used in the brain.⁶ Even though feasibility has been demonstrated in the kidneys,^{7,8} a key challenge for ASL MRI is the inherently limited signal-to-noise ratio (SNR) necessitating repeated measurements to allow data averaging.⁹ This is a major hurdle in the abdomen, because breath holding limits the number of averages that can be performed. Although the feasibility of renal perfusion MRI with ASL has been demonstrated using breath-hold acquisitions in healthy subjects,⁷ it is more

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challenging in patients with compromised renal perfusion. Coached breathing^{10–12} or navigator gated acquisitions¹³ have been used. Navigator gating involves additional data acquisition to estimate the motion that can be used to decide whether to accept or reject the measurement. In prospective gating, this decision is made in real time. In retrospective gating, a fixed number of data acquisitions are made, and accept or reject decisions are made retrospectively. In this study, we have evaluated renal perfusion using a retrospectively navigator gated ASL MRI sequence¹³ in a sufficiently large number of subjects with chronic kidney disease and healthy controls with no known renal disease.

METHODS

Study Subjects

All procedures were performed with approval from the institutional review board and written subject consent prior to enrollment. MRI data were acquired in a group of diabetic patients with stage 3 CKD ($n = 33$) and healthy subjects ($n = 30$) with no known renal disease. Subjects were instructed not to take nonsteroidal anti-inflammatory drugs for 3 days and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers 1 day prior to MRI. Both groups were instructed to fast after midnight on the day of the MRI and to take one-half the dose of insulin if applicable. Blood was drawn for estimated glomerular filtration rate (eGFR) calculation either on the day of the scan for healthy subjects or during the screening visit prior to the MRI scan for patients. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for eGFR calculation.¹⁴ Twenty-four-hour urine samples were collected within a few days after MRI in most of the patients with CKD (28/33) for analysis of urine creatinine and protein excretion.

Because data were acquired in the fasted status, in 8 of the healthy subjects (30.6 ± 11.1 years), we also evaluated any potential effect of hydration on ASL-derived perfusion measurement on a separate day. For these studies, subjects followed the same preparation as above. Urine-specific gravity was used to document the subject's hydration status. Urine samples were acquired prior to the baseline scan, and 1 sample following each MRI acquisition after water loading. Following the ASL baseline scan, subjects drank water based on their body weight (20 ml/kg) within 15 minutes. After water loading, ASL MRI data were acquired 2 times.

MRI Acquisition Methods

All the studies were performed on a 3.0T MRI system (MAGNETOM Verio, Siemens Healthcare, Erlangen,

Germany) equipped with high-performance gradient coils (45 mT/m maximum gradient strength, 200 mT/m/ms slew rate). The body coil was used as the transmitter, and the combination of spine and body array coils was used as the receiver. Subjects were positioned feet first and supine.

The renal perfusion measurement was performed using the 2-dimensional navigator-gated FAIR True-FISP sequence.¹³ A 10.24-millisecond adiabatic frequency offset corrected inversion (FOCI) pulse ($\mu = 6$, $\beta = 1078$) was used for selective inversion.¹⁵ The scan prescription included the following: (i) defining the imaging slice (thickness = 8 mm) position in an oblique coronal orientation to match the longitudinal axis of both kidneys; (ii) positioning a slice selective inversion band (thickness = 30 mm) over the imaging slice, with care taken to avoid intersection with major arteries; and (iii) choosing the slice position for the navigator in the coronal plane. To allow sufficient labeled blood to perfuse into the tissue, an inversion pulse delay time (TI) of 1.5 seconds for healthy controls or 2.0 seconds for patients was used.¹³ The imaging readout used a true fast imaging with steady precession sequence (TR/TE = 4.0/2.02 milliseconds; FA = 60°; field of view = 360–400 mm; matrix = 128 × 128; BW = 651 Hz/pixel). The 2-dimensional navigator acquisition was performed immediately following the imaging readout using a fast low angle shot (FLASH) readout (TR/TE = 2.2/1.2 ms; FA = 5°; field of view = 400 × 400 mm²; matrix = 96 × 96; BW = 1000 Hz/pixel; generalized autocalibrating partially parallel acquisitions [GRAPPA] factor = 2).

The acquisition efficiency of this 2-dimensional navigator in a previous study was about 35% (range, 26%–39%) in patients and 50% (range, 35%–65%) in healthy subjects, depending on the respiratory pattern.¹³ To maintain protocol consistency, we took a conservative approach and acquired 50 control/label pairs of perfusion weighted images with a total scan time of 5 minutes in healthy subjects and 100 control/label pairs of perfusion weighted images with a total scan time of 10 minutes during free breathing in subjects with CKD. A proton density-weighted (M0) image was acquired using an identical True-FISP readout with a pulse repetition time of 10 seconds and no inversion pulse.

MRI Analysis Methods

ASL maps were reconstructed using a MATLAB (MathWorks, Natick, MA) based custom suite of software.¹³ Navigator data was used to estimate the translational motion in the coronal plane. Only images where the diaphragm position was within the acceptance window (8-mm width) were selected for the perfusion calculation. This processing scheme leads to a variation in the final number of selected control and

label images for each subject. Selected images were further realigned using the FMRIB's Linear Image Registration Tool (FLIRT, FMRIB, Oxford, UK).¹⁶ The first image of each sequence was used as the reference, and the remaining images were aligned with it. Control and label images were then separately averaged to yield a single control image and a single label image. The final perfusion weighted image was computed by subtracting the averaged control from the averaged label image. Quantitative renal blood flow was calculated pixel-by-pixel using a single compartment model¹⁷:

$$f = \frac{\lambda}{2\alpha T_1} \frac{\Delta M(TI)}{M_0} \exp\left(\frac{-TI}{T_1}\right)$$

where f is the perfusion rate (in the unit of ml/100 g/min), λ is the blood–tissue–water partition coefficient, which was assumed to be 80 ml/100 g,¹⁸ α is the inversion efficiency, which was assumed to be 0.95, $\Delta M(TI)$ is the perfusion weighted image, and M_0 is the equilibrium magnetization of the tissue (proton density). The T_1 value of 1.15 seconds for the renal cortex¹⁹ is assumed to be the T_1 of the blood.

Regions of interest (ROIs) were manually defined in the cortex and medulla on ASL maps to calculate blood flow using a custom image processing toolbox written in Python (Python Software Foundation, Wilmington, DE).^{20,21} ROIs were defined in the cortex and medulla for both the left and right kidneys. Tumors and cysts were excluded from the ROIs. The cortical ROI was defined as 1 large ROI (>500 voxels) encompassing the vast majority of the cortex. Medullary ROIs were drawn using a freehand tool and typically consisted of less than 100 voxels. After all the ROIs were defined for both kidneys in each subject, the mean value of each region was computed to obtain 1 representative value per subject per region (cortex and medulla).

Statistical Methods

A 2-sample t test or Wilcoxon rank sum test (if normality in distribution was not observed) was used to compare the various MRI-derived parameters, along with age and eGFR, between the CKD and control groups. We included Cohen's d as the measure of the magnitude of difference between groups. Cohen's d represents the effect size, and in this study we recognize 3 levels: small, medium, and large. These levels correspond to d values greater than or equal to 0.2, 0.5, and 0.8, respectively.²²

Spearman correlation coefficients were calculated among the following variables: cortical blood flow (Cor_BF), medullary blood flow (Med_BF), eGFR, age, and body mass index (BMI). P values are reported for all statistical tests. Linear regression was used to explore the pairwise relationship between Cor_BF,

Med_BF, and eGFR. Multiple linear regressions were used to explore the pairwise relationship accounting for any potential confounding effect of age, gender, race, or BMI where appropriate. The confounder was retained in the model if it changed the regression coefficient of eGFR more than 15%. Parameter estimate, SE, and P values were reported for the regression analyses.

Aside from the regression analysis, the confounding effects (if any) in the above-mentioned analysis were removed by conducting a 1:1 age, gender, race, or BMI matching between the CKD and control groups. The propensity score matching method used a greedy 8-to-1 matching algorithm for identifying matched pairs.

The Cor_BF and Med_BF readings from the 2 groups were used to assess whether ASL measurement could be used to discriminate CKD from healthy subjects. The optimal thresholds for Cor_BF and Med_BF were determined by conducting a receiver operating characteristic (ROC) analysis using each measure (Cor_BF and Med_BF) alone as a continuous variable to distinguish abnormal perfusion in CKD from normal subjects. Areas under the curve were estimated with a 95% confidence interval. Sensitivity and specificity for the optimal threshold for each measure were determined by the Youden Index.

Repeated-measures analysis of variance was used to compare the changes from baseline for Cor_BF and specific gravity for water-loading results. Multiple comparisons were adjusted.

All of the statistical analyses were carried out in SAS 9.3 (SAS Institute, Cary, NC), and a P value of <0.05 was regarded as statistically significant.

RESULTS

A total of 33 patients with CKD and 30 control subjects participated in our study (Table 1). The median eGFR and 24-hour urine protein excretion in patients was 46.7 ml/min/1.73 m² and 0.18 g, respectively (Table 2). However, most of the subjects with CKD were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. There were significantly higher proportion of female patients in the CKD group than in the healthy control group (54.6% vs. 20%, $P = 0.0048$). The 2 groups had similar proportions of African American to white subjects.

Table 1. Gender, race, and medication in study participants

	N	Male: Female	Race (AA:C:O)	Medications
CKD	33	18:15	11:22:0	ACEI/ARB (n = 23)
Control	30	6:24	10:16:4	n/a

AA, African American; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C, Caucasian; CKD, chronic kidney disease; n/a, not applicable; O, other.

Table 2. Interquartile range of age, BMI, eGFR, and urine protein

Parameter	Group	n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
Age	CKD	33	68.1	9.0	69.4	61.0	74.8
	Control	30	42.0	18.1	42.7	22.5	55.0
BMI (kg/m ²)	CKD	33	31.8	6.3	30.1	27.3	35.8
	Control	30	24.5	3.3	23.3	22.8	26.4
eGFR (m/min/1.73 m ²)	CKD	33	50.0	13.9	46.7	39.3	62.9
	Control	30	100.7	17.7	101.9	87.0	111.6
Urine protein (g)	CKD	28	1.86	4.6	0.175	0	1.045
	Control	n/a	n/a	n/a	n/a	n/a	n/a

BMI, body mass index; eGFR, estimated glomerular filtration rate; n/a = not available; Q, quartile.

Figure 1 shows representative renal perfusion maps from a healthy subject and a subject with CKD. The color bar shows the blood flow in units of milliliters per minute per 100 g. One can appreciate the lower renal blood flow in the subject with CKD compared to the healthy subject.

Table 3 summarizes variables in this study based on groups. All variables age, eGFR, BMI, Cor_BF, and Med_BF were significantly different between CKD and controls (P values < 0.0001 , d values > 1.4 [range, 1.4–3.19]). In addition, there was no difference between left and right kidneys in both the CKD and control groups (data not shown).

Table 4 shows all pairwise correlation among the variables age, eGFR, Cor_BF, Med_BF, and BMI. Because age, Cor_BF, and Med_BF were correlated with eGFR, a

regression analysis was conducted to test for potential confounding effect of age, race, gender, and BMI on the relationship between blood flow with eGFR. Table 5 shows the results of the linear regression for both Cor_BF and Med_BF against eGFR. Age and BMI were found to be confounding factors by multiple linear regression analysis for Cor_BF but not Med_BF (Table 6) based on changes in the regression coefficient of BF versus eGFR of more than 15%. The results of the ANOVA are in the Supplementary Tables. Table 7 shows the comparison between CKD and healthy controls for age- and BMI-matched pairs of subjects. All 3 parameters eGFR, Cor_BF, and Med_BF showed significant differences between CKD and healthy control subjects, even though the sample size was small ($n = 6$).

The optimal threshold to separate CKD and healthy for Cor_BF was estimated to be 142.9 (Youden Index = 0.85) and Med_BF was 24.1 (Youden Index = 0.64). The sensitivity and specificity for this threshold were 84.85% and 100.00% for Cor_BF and 60.61% and 100.00% for Med_BF. The accuracy was estimated by the area under the ROC curve. The area under the ROC curve for Cor_BF was 0.98, which is rated as excellent, and for Med_BF was 0.88, which is rated as good.

Even though specific gravity showed significant reduction after water loading compared to baseline (1.00 ± 0.01 vs. 1.03 ± 0.0 , $P < 0.0001$), there was no difference in Cor_BF (208.1 ± 33.4 vs. 193.9 ± 26.7 ,

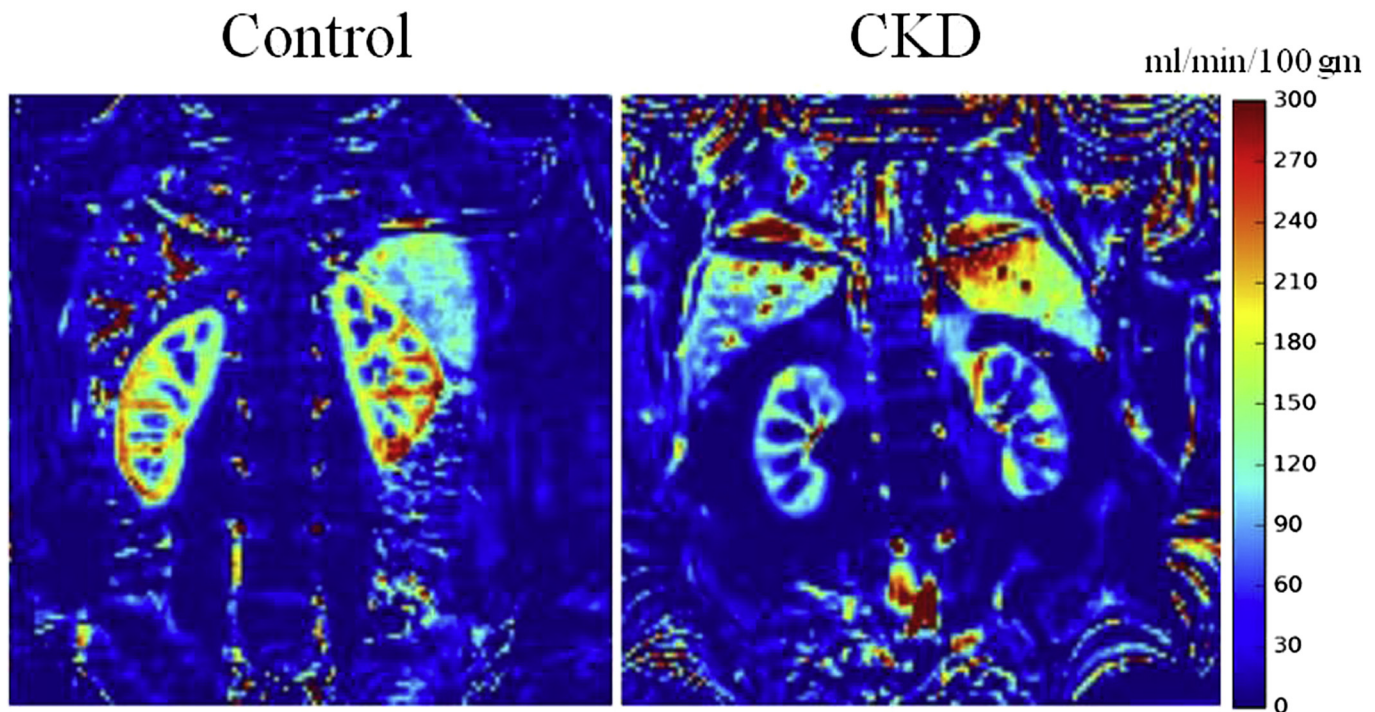


Figure 1. Representative images obtained with retrospective 2-dimensional navigator gated arterial spin labeling (ASL) sequence. On the left is the ASL perfusion map from a healthy control subject, and on the right is one from a subject with chronic kidney disease (CKD). The window and level settings were the same for both. Note the reduced blood flow in the subject with CKD compared to the control subject.

Table 3. Characteristics of CKD and healthy control subjects at baseline

Parameter	Health status	n	Mean	SD	P value	d Value
Age	CKD	33	68.1	9.0	<0.001	1.83
	Healthy	30	42.0	18.1		
BMI	CKD	33	31.7	6.3	<0.001	1.4
	Healthy	30	24.5	3.3		
eGFR	CKD	33	50.0	13.9	<0.001	3.19
	Healthy	30	100.7	17.7		
Cor_BF	CKD	33	108.4	36.4	<0.001	2.52
	Healthy	30	207.3	41.8		
Med_BF	CKD	33	23.2	8.9	<0.001	1.5
	Healthy	26	42.6	15.8		

BMI, body mass index; CKD, chronic kidney disease; Cor_BF, cortical blood flow; eGFR, estimated glomerular filtration rate; Med_BF, medullary blood flow.

$P = 0.34$) and Med_BF (90.6 ± 32.2 vs. 91.9 ± 18.4 , $P = 0.99$), suggesting that hydration may not have a significant influence on ASL-derived renal perfusion estimates.

DISCUSSION

Blood flow to the kidneys is thought to be reduced with progression of CKD.² The conventional method for measuring renal blood flow is the para-aminohippurate clearance method.²³ This is invasive and time consuming and hence only used for research purposes. Contrast-enhanced MRI²⁴ and computed tomography²⁵ methods can be used to measure renal blood flow; however, they are contraindicated in patients with CKD.⁵ Nuclear medicine-based methods are available to estimate renal blood flow²⁶ but are not widely used in the clinic. Overall, there are very few data available on renal blood flow in subjects with CKD. A recent study used phase contrast MRI to measure blood flow within renal arteries in subjects with CKD, and found that the flow was reduced by about 28% and measured GFR was reduced by 37%.²⁷

Prior studies have demonstrated the feasibility of acquiring ASL perfusion MRI measurements in the kidneys^{7,8} and preliminary data showed differences between subjects with CKD and healthy controls with small

Table 4. Summary of Spearman correlation coefficients (ρ)

	Age	eGFR	Cor_BF	Med_BF	BMI
Age	1	-0.62	-0.58	-0.39	0.47
P value		<0.0001	<0.0001	0.0028	<0.0001
eGFR		1	0.67	0.62	-0.58
P value			<0.0001	<0.0001	<0.0001
Cor_BF			1	0.70	-0.55
P value				<0.0001	<0.0001
Med_BF				1	-0.38
P value					0.0029
BMI					1

BMI, body mass index; Cor_BF, cortical blood flow; eGFR, estimated glomerular filtration rate; Med_BF, medullary blood flow.

Table 5. Multiple linear regression analysis with eGFR as independent and BF as dependent variable

Region	Parameter	Estimate	SE	P value
Cor_BF	Intercept	54.70	14.61	0.0004
	Slope (eGFR)	1.33	0.18	<0.0001
Med_BF	Intercept	10.42	3.87	0.0092
	Slope (eGFR)	0.28	0.05	<0.0001

BF, blood flow; Cor_BF, cortical blood flow; eGFR, estimated glomerular filtration rate; Med_BF, medullary blood flow.

numbers of subjects.^{13,28} Although only a few studies evaluating ASL MRI measurements have been performed to date, the technique has been shown to be reproducible.^{29,30} Furthermore, ASL MRI-derived perfusion estimates correlated well with para-aminohippuric acid measurements and were able to discriminate pharmacologic changes in renal plasma flow.³¹ The comparison of the ASL technique with a microsphere method in an animal model has shown that cortical perfusion measured with ASL correlated with microspheres in the expected physiologic range.³² In a group of 98 transplant recipients, ASL MRI identified reduced cortical blood flow in subjects with reduced renal function ($eGFR \leq 30$ ml/min/1.73 m²) compared to those with good-to-moderate renal function ($eGFR > 30$ ml/min/1.73 m²).³³

Consistent with previously reported data, our data show a significant reduction in cortical and medullary blood flow in subjects with CKD compared to healthy controls in a moderately large number of subjects. We further observed a significant correlation of renal blood flow with eGFR. Cortical blood flow and eGFR were reduced by ~50% in subjects with CKD compared to controls. Multiple linear regression analysis found age and BMI to be confounders for cortical blood flow. However, within the age- and BMI-matched group, the difference in eGFR and renal blood flow between CKD still remained significant.

Proteinuria is a common clinical signature observed in patients with diabetic nephropathy. In our study, the median value of 24-hour urine protein was relatively low (0.175 g), probably due to the use of

Table 6. Multiple linear regression analysis with eGFR as independent and BF as dependent variable with adjustment for age and BMI

Region	Parameter	Estimate	SE	P value
Cortex	Intercept	143.49	50.01	0.0057
	Slope (eGFR)	0.99	0.26	0.0004
	Slope (age)	-0.38	0.39	0.345
	Slope (BMI)	-1.50	1.04	0.1561
Medulla	Intercept	15.11	13.50	0.2682
	Slope (eGFR)	0.27	0.07	0.0004
	Slope (age)	0.02	0.10	0.8469
	Slope (BMI)	-0.18	0.28	0.5307

BF, blood flow; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Table 7. Summary of age- and BMI-matched groups

Parameter	Health Status	n	Mean	SD	P value
Age	CKD	6	63.22	7.15	0.6884
	Healthy	6	65.07	9.86	
BMI	CKD	6	25.89	3.34	0.6408
	Healthy	6	25.02	2.93	
eGFR	CKD	6	45.73	11.72	<0.0001
	Healthy	6	92.76	11.36	
Cor_BF	CKD	6	107.4	42.8	0.002
	Healthy	6	187.51	20.44	
Med_BF	CKD	6	15.43	8.43	0.0019
	Healthy	6	39.18	11.13	

BMI, body mass index; CKD, chronic kidney disease; Cor_BF, cortical blood flow; eGFR, estimated glomerular filtration rate; Med_BF, medullary blood flow.

angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers.

Renal blood flow in CKD patients is about one-half of that in healthy controls in both the renal cortex (108.4 ± 36.4 vs. 207.3 ± 41.8 ; $P < 0.001$, $d = 2.52$) and medulla (23.2 ± 8.9 vs. 42.6 ± 15.8 ; $P < 0.001$, $d = 1.5$). Because we performed studies following an overnight fast, we wanted to determine whether hydration status would have any significant influence on renal blood flow as evaluated by ASL. In a small sub-study, we looked at the effect of water loading in fasted healthy subjects on ASL measurements. Although the urine specific gravity changed significantly after water loading, the renal perfusion estimates did not change. This suggests that ASL MRI-based perfusion estimates may not be influenced by hydration status within normal limits.

There are a few limitations to this study. The control group was not age, gender, and BMI matched with the CKD group. Even though age and BMI were found to be confounding factors in the relationship between cortical blood flow and eGFR, when identifying a subgroup with matched age and BMI, both cortical and medullary blood flow were significantly lower in subjects with CKD compared to the control group. The ASL MRI protocol used here required 5 to 10 minutes for data acquisition. Even though these are during free breathing, they could be considered to be long, especially for a single slice acquisition. For this preliminary study, we were conservative and acquired more data than necessary. In a small number of subjects with CKD ($n = 6$), data using only one-half the number of acquired images yielded comparable perfusion estimates (data not shown). These preliminary data could be used to optimize the total acquisition time for future use. Absolute quantification of renal blood flow with the present implementation of ASL has not yet been validated, for example, against microspheres. The current values for cortical perfusion (~ 200 ml/min/100 g) are lower than in our own previous report (~ 260 ml/min/100 g). The key difference

between these 2 studies is that the subjects in the current study fasted before the scan. In fact, that was the motivation to study the potential effects of water loading on renal perfusion. We may need future studies to verify the effects of fasting. Even though a previous study has validated ASL estimated cortical perfusion against microspheres,²³ no such validation is available for medullary blood flow estimates. ASL is inherently limited in sensitivity to low flow. However, the primary interest in routine use demands precision rather than accuracy. A recent report suggests a high degree of reproducibility of renal ASL MRI when repeated after 2 weeks.²⁹ In this study, we used longer TI for patients, assuming slower circulation compared to that of controls.^{13,34} Although this is not ideal, it should not unduly influence the estimated flow, as the quantitation takes TI in to account. In a healthy volunteer, the flow estimates were relatively stable for a range of TI values between 1 and 2 seconds (146.4 ± 15.9 ml/min/100 g). The values for TI outside this range were considerably lower. Future studies may have to include multiple TIs to estimate both average transit times and transit time-corrected blood flow estimates, as suggested by a recent report.³⁴

In conclusion, ASL-derived renal perfusion values were significantly lower in subjects with CKD and correlated with eGFR. Both cortical blood flow and eGFR were reduced about 50% in the CKD group compared to controls. Overall, the data presented here, along with other recent studies support the feasibility of using ASL perfusion MRI in the evaluation of CKD to identify early markers of progression. The significant and large difference between CKD and healthy subjects makes this ASL technique a potential tool to document the change in perfusion in longitudinal studies. Combined with blood oxygenation level-dependent MRI to evaluate relative renal hypoxia and diffusion MRI to evaluate fibrosis,^{3,4} a comprehensive and noninvasive suite of tools may now be available for evaluating the chronic hypoxia hypothesis.² The differences observed here between CKD and control groups are probably smaller compared to differences between progressive CKD patients and control groups, as it has been reported that only one-third of patients with diabetes may show progressive decline in renal function.³⁵

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Tables. Analysis of variance for evaluating the contributions of the confounding factors to renal cortical blood flow.

Supplementary material is linked to the online version of the paper at <http://www.kireports.org>.

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