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Consistency of Multiple Renal Functional MRI Measurements over 18 Months

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Abstract

Background—Identification of patients with progressive chronic kidney disease (CKD) and those likely to respond to candidate therapeutics is urgently needed. Functional MRI measurements have shown promise. However, the knowledge about the consistency of the measurements is essential to conduct longitudinal studies.

Purpose/Hypothesis—To investigate the consistency of repeated functional MRI measurements in healthy subjects.

Study Type—Prospective, longitudinal study.

Subjects—17 healthy subjects were examined on two different occasions, 18 months apart.

Field Strength/Sequence—Multiple gradient-recalled-echo, 2D navigator-gated flow-sensitive alternating inversion recovery True-FISP and spin-echo planar diffusion-weighted sequences were used on a 3T scanner. Images were acquired on two different scanner configurations.

Assessment—Blood oxygenation level dependent (BOLD) R2*, arterial spin labeling (ASL) perfusion derived blood flow (BF) and apparent diffusion coefficient (ADC) maps were analyzed using a custom image processing toolbox. ROIs were placed on renal cortex, medulla, and whole kidney. Multiple researchers were involved in defining the ROIs.

Statistical Tests—Intra- and inter-subject coefficients of variation (CV) and Bland-Altman plots were used to measure consistency and evaluate bias in the measurements. Nonparametric Wilcoxon test was used to compare difference between two time points.

Results—The intra-subject CV for R2* and ADC were 6.8% and 5.3% with small (−3.8 and 5.3%) bias respectively comparing baseline and 18-month data. Intra-subject CV for renal cortex BF was higher (18.7%) compared to R2* and ADC, but comparable to prior literature values over shorter durations. It also exhibited a larger bias (−15.4%) between two time points and significant lower values ($p = 0.022$) at 18 month data.

Data Conclusion—All three MRI parameters over 18 months even with a scanner upgrade and involving multiple observers showed good consistency. These results are useful for the interpretation of longitudinal data and support the use of these methods to monitor progression in patients with CKD.

Keywords

blood oxygenation level dependent; apparent diffusion coefficient; arterial spin labeling; chronic kidney disease; kidney

INTRODUCTION

Disease progression in chronic kidney disease (CKD) happens at variable rates and over a number of years¹. Moreover, only a fraction of the subjects with CKD will progress to end stage renal disease (ESRD)². Therefore, there is an increased interest in performing longitudinal studies to monitor disease progression³, including using multi-parametric renal functional MRI approaches⁴. The need for renal imaging markers is gaining interest and has led to the formation of international consortium such as PARENCHIMA⁵. A key objective of this effort is to develop standardized imaging markers and apply them to a 3 year longitudinal study in patients with diabetic nephropathy.

Over the last decade, the role of chronic hypoxia in the progression of CKD has gained attention mostly based on pre-clinical data⁶. Blood oxygenation level dependent (BOLD) MRI is the only known non-invasive method currently available to evaluate relative oxygenation status of the kidney^{7,8} and can be readily applied to humans. Chronic hypoxia theory also suggests the cause for the increased hypoxia may be the loss of microvasculature⁹. Arterial spin labeling (ASL) perfusion technique has been widely used in the brain¹⁰, and recently applied to kidneys^{11–16}. ASL based renal perfusion MRI has shown reduced blood flow in CKD^{12,16,17}. Hypoxia triggers fibrogenesis which is known to be the hall mark of progressive CKD¹⁸. Apparent diffusion coefficient (ADC) has been shown to strongly correlate with histological measurements of renal fibrosis^{19,20}.

The purpose of this study was to investigate the level of consistency in the multi-parametric MRI measurements obtained over long intervals (18 month period in current study) necessary for conducting longitudinal studies. At these long intervals, the variability may not only represent measurement bias associated with the technique, but potentially also depend on the differences in subjects' physiology, observer variability, changes to the measurement hardware such as due to scanner upgrades *etc.*. Knowledge of this measurement would be necessary when interpreting longitudinal data in patients in the future, *i.e.* what is the minimum change in each parameter that can be thought to be a meaningful change related to the progression of CKD.

MATERIALS AND METHODS

Subjects

All procedures were performed with approval from the institutional review board and written subject consent prior to enrollment. Seventeen healthy subjects (average 46.3 ± 20.3 years old; BMI 25.5 ± 3.7 and estimated glomerular filtration rate (eGFR) = 95.2 ± 14.5 mL/min/1.73m²) with no known renal disease participated in this study. Subjects were instructed to fast after midnight on the night prior to the MRI. Subjects completed two scans, one at baseline and another approximately 18 months later (18.9 ± 1.0 month).

MRI Acquisition

All measurements were performed on a 3.0 Tesla Siemens whole-body scanner (Siemens Healthcare, Erlangen, Germany) with higher 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 placed feet first in supine position. Table 1 shows the detailed MRI sequence parameters used in this study. Due to a scanner upgrade (Magnetom Verio to Skyra^{Fit}), seven subjects were scanned on Verio at baseline and Skyra^{Fit} at the 18 month time point.

A multiple gradient-recalled-echo (mGRE) sequence was used to acquire BOLD images in the coronal plane during breath-holding at end-expiration ⁴.

The renal perfusion images were acquired using a 2D navigator-gated flow-sensitive alternating inversion recovery (FAIR) True-FISP sequence ¹². An oblique-coronal orientation ASL imaging slice was carefully prescribed using the scout image. A 30 mm slice-selective inversion pulse was prescribed over the image slice in order to avoid intersecting major vessels. Fifty healthy/label pairs were alternately acquired. A 10.24 ms adiabatic frequency offset corrected inversion (FOCI) pulse ($\mu = 6$, $\beta = 1078$) was applied for selective inversion ^{12, 21}. To allow sufficient labeled blood to perfuse into the tissue, an inversion pulse delay time (TI = 1.5 s) was used ¹². The imaging readout used a true FISP sequence. A 2D navigator acquisition was performed immediately following the imaging readout using a FLASH readout (TR/TE = 2.2/1.2 ms; FA = 5°; FOV = 400 × 400 mm²; matrix = 96 × 96; BW = 1000 Hz/pixel; GRAPPA factor = 2). Proton density images with no inversion were acquired to measure M_0 .

Quantitative renal blood flow map was calculated pixel-by-pixel using a single compartment model ²²:

$$f = \frac{\lambda}{2\alpha TI} \frac{\Delta M(TI)}{M_0} \exp\left(\frac{-TI}{T_1}\right) \quad (1)$$

where f is the perfusion rate (in the unit of ml/100g/min), λ is the blood–tissue–water partition coefficient, which was assumed to be 80 ml/100g ²³, α is the inversion efficiency, which was assumed to be 0.95, $M(TI)$ 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 cortex²⁴ was assumed to be the T1 of the blood. ASL maps were reconstructed using custom MATLAB (Math Works, Natick, MA, USA) code¹².

Diffusion-weighted imaging was performed using spin-echo planar imaging (EPI). Diffusion sensitizing gradients were applied along three different directions for calculating diffusion trace which is a direction independent measure. Images using five different b values were acquired during free breathing. Five acquisitions were averaged to improve signal to noise ratio and to minimize motion artifacts. Diffusion maps were generated in-line on the scanner.

MRI data Analysis

R2* maps were generated using a custom image processing toolbox using Python (Python Software Foundation). On the magnitude images, a threshold of 20 (a.u.) was used to mask any voxels that decay to the noise floor prior to performing exponential fit to estimate R2*. This was done to minimize the effect of bulk susceptibility artifacts that can distort the estimated value of R2* for each voxel^{4, 25}. Regions of Interests (ROIs) were manually defined in cortex, medulla or whole kidney by researchers JT (5 yrs) and WL (over 25 yrs experience). The inter-reader agreement were assessed in a previous study²⁵. Renal cortex is the outer layer of kidney about 10 mm thick and typically represented by a ring shaped ROI encompassing the entire length of the kidney (Figure 1). The renal medulla is the innermost part of the kidney and split up into a number of sections in humans known as the renal pyramids. Multiple small ROIs were defined to represent medullary tissue. Whole kidney ROIs were defined on entire renal parenchyma without including voxels from areas near strong susceptibility changes or other artifacts. In order to minimize subjectivity, ROIs were defined on the first image of the series of mGRE images (serving as a T1 weighted anatomical image) then copied to R2* map to measure R2*. Cortical R2* (CR2*), whole kidney R2* (KR2*) and medullary R2* (MR2*) were analyzed for BOLD MRI data. A medullary ROIs were typically <100 voxels while the cortical ROI was defined as one large ROI, typically > 500 voxels⁴. The analysis was typically performed close to the time of acquisition. However, researchers did not refer to the baseline analysis when performing the 18 month analysis and sometimes, the baseline and 18 month data were analyzed by a different researcher.

The tool box also facilitated ROI analysis of ASL and ADC maps. Given the concern with the robustness of medullary blood flow estimates¹⁴ and the fact that histological evaluation of fibrosis involves only cortical tissue²⁶, only cortical blood flow (BF) and ADC were reported for ASL and diffusion data.

Statistical Analysis

Mean and standard deviation (SD) values are reported for each measurement. Intra-subject and inter-subject coefficient of variation (CV) was calculated to estimate the consistency or degree of variation of MRI measurements at two time points. Intra-subject CV was calculated based on individual 18 month and baseline mean and SD. Inter-subject CV was calculated based on group mean and SD at each time point. Bland-Altman plots were used to evaluate the level of agreement between two time points for all measurements. The mean

and difference from the two measurements in each individual was used to calculate each point in Bland-Altman plot. Limit of agreement (LOA) is defined as the mean plus and minus 1.96 times the SD of the differences. Percentage bias is defined as: mean difference between 2 measurements (or difference between the means of the two measurements) / mean at baseline • 100. Nonparametric Wilcoxon signed-rank two tailed test was used to compare difference of all measurements between two time points. All analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY). A *p* value less than 0.05 was considered statistically significant.

RESULTS

Figure 1 illustrates typical examples of parametric maps from this study. Definitions of the different ROIs in different kidney tissues used for analyzing R2* maps are illustrated. ADC maps show the least contrast between cortex and medulla, therefore only cortical ADC values are being reported. Even though ASL maps show high cortico-medullary contrast, medullary BF values are not thought to be robust¹⁴ and hence only cortical BF is reported.

Table 2 summarizes MRI measurements at baseline and at 18-month time points. There were no significant differences in R2* and ADC between two measurements; but cortex BF showed significant difference between baseline and 18 month follow-up. The intra-subject CV between two scans is less than 7% for all R2* measurements (*i.e.* cortex, kidney, and medulla) and ADC. The blood flow demonstrated a much larger variation between scans (18.7%). The variations among subjects (inter-subject CV) at two time points for all measurements are typically larger than intra-subject CV in general.

Figure 2 shows the Bland-Altman plots to illustrate the degree of agreement between the baseline and 18-month scans for all measurements. Overall, the bias between baseline and 18 months was small and not significant (CR2* = 5.3%, KR2* = -1.4%, MR2* = -1.4%, and ADC = -3.8%) except for the cortical BF, which exhibited a relatively large and significant bias (-15.4%) between baseline and 18-month scans.

Table 3 is the summary of MRI measurements from 10 subjects (age: 33.2 ± 14.9 years old; eGFR = 95.5 ± 18.3 mL/min/m²) at both baseline and 18 month completed on Verio. The cortex ADC is different between baseline and 18 month (*p*=0.047). Interestingly, the intra-subject CV for R2* and ADC is slightly larger than in Table 2. Table 4 is the summary of MRI measurements from 7 subjects (age: 64.9 ± 9.1 years old; eGFR = 94.6 ± 7.5 mL/min/m²) whose 18 month follow-up were performed on Skyra^{Fit}. The cortex BF is significantly lower with Skyra^{Fit} than with Verio (*p*=0.028). However, the intra-subject CV for R2* and ADC were smaller than cases where data were acquired on a single scanner configuration (Table 3). On the other hand, for cortex BF, the CV was slightly higher.

DISCUSSION

Consistency of a technique is a key factor to demonstrate how well a technique can be used to monitor changes longitudinally. Our results indicate that R2* and ADC measurements were reproducible within 7% over 18 months, even when a large fraction of the subjects were scanned on two different scanner configurations. This is important because scanner

upgrades are part of reality and need to be taken in to account when performing longitudinal studies. Further, there was more than one researcher involved in image analysis, which is also a fact of reality for longitudinal studies. A prior study demonstrated that use of large cortical ROIs and whole kidney ROIs allows for better inter-observer agreement for R2* measurements²⁵.

The intra-subject CV data shown here are consistent or slightly better than prior reports. Prior study with BOLD MRI²⁷ conducted about 9 months apart on a 1.5 T scanner showed a variability about 12%. The previous report for ADC²⁸ showed an intra-subject CV about 6% when performed 1 day or 1 month apart on a 1.5T scanner. Our results indicate about 6% or less in intra-subject CV with a significantly longer interval of 18 month. The large intra-subject CV in cortical BF also agrees with prior reports^{14, 29–31}, even though those studies were repeated with a much shorter interval between two scans from 1 hour³¹, 1 day¹⁴, few days apart to average about 2 weeks apart^{14, 29, 30}.

While scanner upgrade had little effect (or arguably even smaller intra-subject CV) for R2* and ADC, there was a larger effect observed with ASL. The age of the 7 subjects scanned by two different scanner configurations is significantly younger than the age of the 10 subjects scanned on the same scanner at two time points. Although the age is significantly different for subjects scanned with one scanner configuration and by two, their kidney function based on eGFR were not different. Other than that, all factors are similar for each subset. The exact reason for smaller intra-subject CV for R2* and ADC for subjects scanned by two scanner configurations is not yet clear. We can only speculate that the better signal to noise afforded by Skyra^{Fit} could have contributed to the lower inter-subject CV at month 18 and intra-subject CV for subjects scanned by two scanner configurations at baseline and 18 month respectively. ASL sequence is the only custom sequence among the three evaluated here. With the level of hardware changes, there may be a need to fully calibrate the sequence parameters, especially those related to the spin labeling pulses. This indicates the need for perfusion phantoms for testing consistency of the measurements across scanners and sites. Imaging societies such as International Society for Magnetic Resonance in Medicine (ISMRM) and Radiological Society of North America (RSNA) have initiatives to develop phantoms for scanner testing, primarily focused on quantitative measurements³². The phantoms are limited to conventional MRI parameters such as T1, T2 and ADC. Hopefully, these efforts will be extended to other functional parameters such as the ones used here, R2* and tissue perfusion.

Given the general trend with all the three measurements that our long term intra-subject CVs are comparable to those measured at shorter intervals; suggest that the key contributor to the CV is primarily the measurement bias associated with the technique. This is particularly interesting because our study included a scanner upgrade and also involved more than one researcher defining ROIs. The data is not only encouraging, but also necessary in the interpretation of longitudinal renal functional MRI data in subjects with chronic kidney disease where renal function decline over several years.

Since the Bland-Altman plots show the mean $\pm$ 1.96 SD of difference, it could be useful to determine if an individual subject can be distinguished from this healthy control group. On

an individual basis, values outside the range shown in Bland-Altman plots can be interpreted as a subject not belonging to the control group. Significant group differences can be established with smaller differences, depending on the number of subjects. Bland-Altman plots also illustrate any potential bias between the two measurements. Our results show small and insignificant bias for R2* and ADC measurements. However, Cortex BF showed a larger and significant bias. This is mainly due to the lower values measured on Skyra^{Fit} because there was no significant difference between the two measurements where both time points were acquired on Verio. These data (once confirmed in larger number of subjects) can also be used to compensate for any observed bias.

Our study is limited in terms of the number of time points evaluated. This is purely based on a logistical limitation of conducting studies that are 18 months apart. We did not estimate blood T1 for the ASL based blood flow calculations, which could explain to some degree the lower blood flow values in our study compared to earlier reports ^{12, 30}. While accuracy of ASL measurements is important, for longitudinal studies the more critical parameter is the precision or consistency. Further, there are no “reference-standard” measurements available for human renal perfusion estimates. The study also did not include any patients.

In conclusion, our data show that R2* and ADC were consistent within 7% over the 18 month period, even when data were acquired on two different scanner configurations (Magnetom Verio and Skyra^{Fit}) in a subset of subjects and we had more than one observer involved. The variability with ASL derived blood flow measurements is higher than BOLD and ADC, but comparable to prior literature values. The systematic difference in ASL measurements may need to be further evaluated especially after scanner upgrades. It is interesting to note that ASL has been reported to show large and consistent differences between subjects with CKD and controls ^{16, 17}. The advantage of the higher sensitivity seems to be negated by higher variability. The fact that the consistency evaluated here is comparable or better than previous reports performed over short intervals supports the use of these measurements for longitudinal monitoring of progression of CKD. We believe the data provided here would be useful for interpreting longitudinal multi-parametric functional MRI data to monitor progression of CKD.

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Figure 1.

Representative images from this study. Shown are anatomic images (Top), used to define ROIs (as shown in Row 2). Cortex was defined by a semi-circular shaped ROI defined parallel to the kidney outer contour. Renal medulla was sampled by multiple small ROIs within renal pyramids. Whole kidney ROI was drawn following kidney contour including all renal parenchyma and excluding major renal vessels and collecting system. The rest rows are R2*, ADC and ASL maps with color bars. The unit for R2* is s^{-1} ; for ADC is mm^2/s and ASL is $mL/min/100g$.

Figure 2.

Summary of Bland-Altman plots for all measurements. CR2*: cortical R2*; KR2*: kidney R2*; MR2*: medullary R2*. The three horizontal lines in each plot are upper limit of agreement (LOA), mean of difference, and lower LOA respectively. LOA = mean $\pm$ 1.96 SD of difference between two scans. Bias = 100 * (mean difference / inter-subject mean @ baseline).

Table 1

MRI parameters

parameter	Anatomy			Functional		
	Scout	VIBE		BOLD	ASL	DWI
dimension	2D	3D		2D	2D	2D
Slabs		1				
Slices per slab		48				
FOV read	400 mm	380 mm		380 or 400 mm	380 mm	380 or 400 mm
FOV phase	100%	65.60%		100%	100%	100%
slice thickness	8.0 mm	3 mm		5 mm	8 mm	5 mm
TR	7.0 ms	3.47 ms		50 ms	3000 ms	3000 ms
TE	2.66 ms	1.58 ms		3.1, 7.0, ..., 30.5 ms	1.92 ms	78 ms
Average	2	1		1	1	5
Concatenations	24	1		5	1	1
Flip angle	20°	9°		30°	60°	
Diffusion mode						3 scan trace
diff. directions						3
diff. weightings						5
Lines per shot		34				
Measurements	1	1		1	50	1
Base resolution	256	320		256	128	192
Phase resolution	60%	60%		100%	100%	80%
interpolation	on	off		off	off	off
Slice resolution		63%				
Phase partial Fourier	off	6/8		off	off	6/8
Slice partial Fourier		7/8				
PAT mode	None	GRAPPA		None	None	GRAPPA
# of Slice	8			5	1	5
dist. Factor	50%	20%		0%	20%	0%
Concatenations	24	1		5	1	1
Segments	1			1	128	

parameter	Anatomy			Functional		
	Scout	VIBE		BOLD	ASL	DWI
Contrast	1	1		8	1	
Bandwidth	290 Hz/pixel	780Hz/pixel		260 Hz/pixel	501 Hz/pixel	1628 Hz/ pixel
Echo spacing					3.8 ms	0.68 ms
Inversion delay					1500 ms	
b values (s/mm ²)						200, 300, 500, 700, 1000 ms
accel. Factor PE		2				2
ref. lines PE		24				24
phase oversampling		30%			0%	
slice oversampling		16.7%				

Table 2

Summary of MRI measurements in 17 healthy subjects at baseline and 18 month

Variable	Baseline			18 Month		
	Mean	SD	inter-CV	Mean	SD	inter-CV intra-CV
Cortical R2*	18.8	2.0	10.8	19.8	1.8	9.2 6.8
Kidney R2*	22.2	1.6	7.2	22.0	1.8	8.0 4.4
Medullary R2*	28.7	2.9	10.0	28.3	1.9	6.5 6.6
Cortical ADC	1589.2	143.8	9.0	1529.2	195.7	12.8 5.3
Cortical BF	191.2	33.6	17.6	161.7*	37.4	23.2 18.7

* : significant difference between baseline and 18 month by Non-parametric Wilcoxon signed-rank two tailed test. p = 0.022. The unit for R2* is s⁻¹; for ADC is mm²/s; for cortex BF is ml/min/100g.

Table 3

Summary of MRI measurements in 10 healthy subjects with Verio at baseline and 18 month

Variable	Baseline			18 Month		
	Mean	SD	inter-CV	Mean	SD	inter-CV
Cortical R2*	17.9	1.4	8.1	19.6	2.0	10.3
Kidney R2*	21.6	1.3	6.2	21.6	1.8	8.4
Medullary R2*	28.1	3.1	11.0	27.3	1.4	5.1
Cortical ADC	1599.5	181.2	11.3	1498.3*	232.0	15.5
Cortical BF	192.4	40.8	21.2	172.1	29.9	17.4

* : significant difference between baseline and 18 month by Non-parametric Wilcoxon signed-rank two tailed test. $p = 0.047$. The unit for R2* is s^{-1} ; for ADC is mm^2/s ; for cortex BF is $ml/min/100g$.

Summary of MRI measurements in 7 healthy subjects with Verio at baseline and Skyra^{Fit} at 18 month

Table 4

Variable	Baseline			18 Month		
	Mean	SD	inter-CV	Mean	SD	inter-CV
						intra-CV
Cortical R2 [*]	20.0	2.2	11.0	19.9	1.6	8.1
Kidney R2 [*]	23.1	1.7	7.3	22.5	1.6	7.2
Medullary R2 [*]	29.6	2.5	8.4	29.7	1.6	5.3
Cortical ADC	1574.5	73.9	4.7	1573.3	132.3	8.4
Cortical BF	189.6	22.8	12.0	146.9 [*]	44.2	30.1
						20.6

* : significant difference between baseline and 18 month by Non-parametric Wilcoxon signed-rank two tailed test. p = 0.028. The unit for R2* is s⁻¹; for ADC is mm²/s; for cortex BF is ml/min/100g.