An Arterial Spin Labeling Approach to Kidney Perfusion: Assessing Reproducibility in Native and Transplanted Kidneys

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INTRODUCTION: Magnetic Resonance Imaging (MRI) may be more sensitive to nephron loss than current clinical parameters while also providing a non-invasive test to follow disease progression. Due to the risk of Nephrogenic Systemic Fibrosis (NSF) associated with contrast-enhanced perfusion techniques in subjects with renal failure, non-contrast enhanced MRI perfusion techniques are preferable. Arterial Spin Labeling methods allow perfusion measurement without injecting exogenous contrast agents (e.g. gadolinium) by magnetically labeling the endogenous blood. The purpose of this study was to determine intra-day and inter-day reproducibility of an ASL perfusion technique in the cortex of both native and transplant kidneys. Additionally, native and transplant cortical perfusion were compared and correlated to estimated glomerular filtration rate (eGFR).

MATERIALS AND METHODS: This HIPAA compliant study was approved by our institutional human subjects review committee and written informed consent was obtained from all subjects. We recruited 10 native subjects and 15 transplant subjects, over a broad range of renal function. Two MR perfusion examinations were performed on two separate days (day 1 and day 2) which were at least 24 hours apart. The eGFR was measured on each day, just prior to the MR scanning session. Perfusion measurements were also repeated within the same day, immediately following the first exam, in 8 native subjects (on day 2) and in 12 transplant subjects (on day 1 and 2). Subjects refrained from fluids for four hours prior to examination.

ASL Acquisition ASL cortical perfusion images were acquired on a 1.5 T MR scanner (GE Healthcare) following a 1.2 second delay time using a FAIR-bSSFP technique [1] (parameters: TR/TE/flip = 4.6/2.3ms/70°, BW = 83.33 kHz, FOV = 34-36 cm, and matrix = 128 x 128, slice thickness = 8 mm). Respiratory coaching was provided prior to the scan and imaging was triggered during the expiration phase until 32 control-tag image pairs were acquired. Several proton density images were also acquired for normalization. (scan time: ~6-9 minutes)

Segmentation and Processing ASL perfusion exams were analyzed with a one compartment ASL model using custom scripts written in MATLAB (version 7.5, The MathWorks Inc.). After automatically aligning each kidney in the image series using Normalized Mutual Information (NMI), the cortex was manually segmented using interactive threshold techniques. The average difference between control and tag was used to calculate perfusion based on known scan parameters and assumed values of T1 = 966ms [2], and partition coefficient, λ = 80 ml/100g. ASL perfusion measurements from all the cortical pixels were averaged for each kidney.

Statistical Analysis Intra-class correlations (ICC) and coefficients of variation (CV) were calculated as metrics of reproducibility. Additionally, groupwise perfusion comparison was performed on measurements from day 1 after dividing the subjects into two groups: healthy normal function denoted by an eGFR above 60 ml/min/1.73m^2 and poor function with eGFR below 60 ml/min/1.73m^2. Differences between native and transplant subjects in the same eGFR group were determined using the Wilcoxon rank sum test and are shown with dot plots. For native subjects, left and right cortical kidney perfusion measurements were averaged for groupwise comparison and correlation to eGFR. Correlation to eGFR was determined from day 1 measurements. Both Pearson (r) and Spearman (r_s) coefficients were calculated in all correlation analyses.

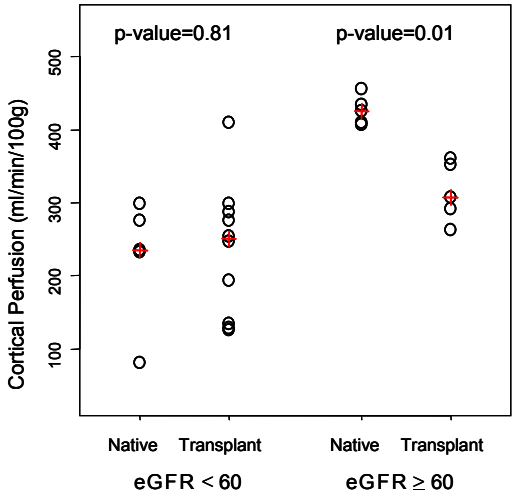
RESULTS AND DISCUSSION:

Table 1: Intra-day and Inter-day Cortical Perfusion Comparison: Correlation, ICC, and CV

		r	r_s	ICC	CV(%)
Intra-day Perfusion Comparison					
Native	Right kidney at day 2 (n=8)	0.95*	0.81**	0.92	8.5
	Left kidney at day 2 (n=8)	0.93*	0.93*	0.90	9.9
Transplant	day 1(n=12)	0.97*	0.90*	0.96	5.3
	day 2 (n=12)	0.95*	0.86*	0.95	6.8
Inter-day Perfusion Comparison					
Native	Right kidney (n=9‡)	0.88*	0.63***	0.89	11.0
	Left kidney (n=10)	0.89*	0.78*	0.89	13.1
Transplant	Cortical (n=14§)	0.93*	0.94*	0.94	7.6

*p-value<0.01; **p-value<0.05; ***0.05<p-value<0.1 ‡ intra-exam motion was too severe for rigid registration in 1 of 10 native right kidneys on day 1. § One of the 15 transplant subjects was unable to return for an exam on day 2 due to health complications.

Figure 1: Day 1 Perfusion for Native and Transplant Subjects with eGFR above and below 60 ml/min/1.73m^2



Intra-day cortical perfusion comparisons demonstrated ICC's of 0.92 and 0.90 for the native right and left kidneys respectively. Intra-day ICC's of 0.96 and 0.95 were demonstrated for transplanted kidneys on day 1 and 2 respectively. Respective CV's were 8.5%, 9.9%, 5.3%, and 6.8%. (**Table 1**) Inter-day measurements demonstrated ICC's of 0.89, 0.89, and 0.94 for the native right kidneys, native left kidneys, and transplanted kidneys. Respective CV's were 11.0%, 13.1%, 7.6%. (**Table 1**) Groupwise comparison (**Fig. 1**) indicated a statistical difference in perfusion between native and transplant subjects with an eGFR $\geq$ 60 ml/min/1.73m^2 (p=0.01). This may result from differential regulation of blood flow in transplanted kidneys or the vasoconstrictive effects of calcineurin inhibitors that are commonly used in kidney transplantation to prevent rejection and is an area of future study. A perfusion difference was not observed between native and transplant subjects with poor function (eGFR $\leq$ 60 ml/min/1.73m^2). As expected, cortical perfusion correlated with eGFR in both native (r = 0.85, p = 0.002; *r_s=0.76, p=0.01*) and transplanted kidneys (r = 0.61, p = 0.015; *r_s=0.57, p=0.03*). Several poorly functioning transplanted kidneys as determined by eGFR had similar or even higher perfusion than healthy, normal transplanted kidneys (**Fig 1**), leading to the lower correlation between perfusion and eGFR. This suggests that blood flow and eGFR are not regulated to the same degree in a transplanted kidney compared to a native kidney.

CONCLUSIONS: This ASL-FAIR perfusion method is reproducible in the cortex of the kidney and may be useful for the longitudinal assessment of transplant function. Studies with larger patient populations are currently being conducted to determine the diagnostic potential of this technique for early detection of chronic rejection. Future work will examine medullary perfusion measurement using this ASL technique.

REFERENCES: [1] Martirosian *et al.* Magn Reson Med. 2004; 51(2): 353-61. [2] de Bazelaire *et al.* Radiology. 2004; 230: 652 659.
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