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Technical note

# Renal plasma flow (RPF) measured with multiple-inversion-time arterial spin labeling (ASL) and tracer kinetic analysis: Validation against a dynamic contrast-enhancement method

Christopher C. Conlin [a,b], Niels Oesingmann [c], Bradley Bolster Jr [d], Yufeng Huang [e], Vivian S. Lee [a], Jeff L. Zhang [a,b,*]

[a] Department of Radiology and Imaging Sciences, University of Utah, 729 Arapeen Drive, Salt Lake City, UT 84108, USA
[b] Department of Bioengineering, University of Utah, 36 S Wasatch Drive, Rm 3100, Salt Lake City, UT 84112, USA
[c] Siemens Medical Solutions, Inc., 660 First Avenue, 4th Floor, New York, NY 10016, USA
[d] Siemens Medical Solutions, Inc., 729 Arapeen Drive, Salt Lake City, UT 84108, USA
[e] Division of Nephrology, Department of Internal Medicine, University of Utah, 30 N 1900 E, Rm 4R312, Salt Lake City, UT 84132, USA

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ABSTRACT

*Purpose:* To propose and validate a method for accurately quantifying renal plasma flow (RPF) with arterial spin labeling (ASL).
*Materials and methods:* The proposed method employs a tracer-kinetic approach and derives perfusion from the slope of the ASL difference signal sampled at multiple inversion-times (TIs). To validate the method's accuracy, we performed a HIPAA-compliant and IRB-approved study with 15 subjects (9 male, 6 female; age range 24–73) to compare RPF estimates obtained from ASL to those from a more established dynamic contrast-enhanced (DCE) MRI method. We also investigated the impact of TI-sampling density on the accuracy of estimated RPF.
*Results:* Good agreement was found between ASL- and DCE-measured RPF, with a mean difference of 9 ± 30 ml/min and a correlation coefficient R = 0.92 when ASL signals were acquired at 16 TIs and a mean difference of 9 ± 57 ml/min and R = 0.81 when ASL signals were acquired at 5 TIs. RPF estimated from ASL signals acquired at only 2 TIs (400 and 1200 ms) showed a low correlation with DCE-measured values (R = 0.30).
*Conclusion:* The proposed ASL method is capable of measuring RPF with an accuracy that is comparable to DCE MRI. At least 5 TIs are recommended for the ASL acquisition to ensure reliability of RPF measurements.


## 1. Introduction

Renal perfusion, often reported as renal plasma flow (RPF), has been shown to be a valuable parameter for assessing renal diseases including chronic kidney disease [1], renal artery stenosis [2], and diabetic nephropathy [3,4]. Para-aminohippurate (PAH) clearance methods for measuring RPF [5,6] involve complicated procedures requiring urine collection and blood sampling [7], and do not measure RPF separately for the individual kidneys. Dynamic contrast-enhanced (DCE) techniques record tracer enhancement in the renal tissues using either computed tomography (CT) [8] or magnetic resonance imaging (MRI) [9–11], and quantify tissue perfusion from the dynamic images with tracer kinetic modeling. Despite the reliability of DCE techniques, they require the injection of contrast agents that are either radioactive or have been linked to the development of nephrogenic systemic fibrosis (NSF) [12].

Arterial spin labeling (ASL) MRI was proposed to measure tissue perfusion without the use of any exogenous contrast agents [4,13,14]. In ASL, the magnetization of blood flowing into the tissue is modified, thereby acting as an endogenous contrast agent. A number of different ASL schemes have been proposed, such as the pulsed ASL technique called flow-sensitive alternating inversion recovery (FAIR) [15,16]. In FAIR, two otherwise identical images are acquired following different inversion pulses; one after a spatially non-selective (NS) inversion, and the other after the inversion of a slab slightly thicker than and centered on the imaging slice (referred to as the slice-selective or SS inversion). The time delay between inversion and image readout is called the inversion time (TI). Subtraction of the two images (SS – NS) nullifies signal from static tissue, leaving only signal from inflowing blood. Essentially, the difference between the SS and NS images is a perfusion-weighted image analogous to the contrast-enhanced images from DCE MRI.

However, quantification of tissue perfusion from ASL data is more challenging than from DCE MRI data. First, the ASL difference signal is

* Corresponding author at: Radiology Research, 729 Arapeen Drive, Salt Lake City, UT 84108, USA.
*E-mail addresses:* christopher.conlin@utah.edu (C.C. Conlin), niels.oesingmann@siemens.com (N. Oesingmann), bradley.bolster@siemens.com (B. Bolster), yufeng.huang@hsc.utah.edu (Y. Huang), vivian.lee@hsc.utah.edu (V.S. Lee), lei.zhang@hsc.utah.edu (J.L. Zhang).

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weak [17,18] and decays within 3–5 s due to $T_1$ relaxation [19]. With such low and decaying signal intensity, artifacts from respiratory motion or unequal NS and SS inversion-efficiencies can introduce large errors into ASL perfusion estimates. Furthermore, the signal difference depends heavily on the time interval between labeling and imaging, i.e., the inversion time (TI) [19,20]. These challenges prompt us to follow the approach taken by Buxton et al. [19] and acquire ASL data at multiple TI values. Similar to the idea of dynamic imaging, ASL data acquired at multiple time points can be analyzed using a tracer kinetic approach so that the above confounding factors can be properly considered based on their temporal characteristics, thereby enabling the accurate quantification of tissue perfusion.

In this study, we propose to quantify renal perfusion from multiple-TI ASL data using a tracer kinetic approach. For a group of human subjects, renal perfusion estimates from ASL were compared to those from DCE MRI. Using the same data, we also investigated the impact of TI sampling density on the accuracy of perfusion estimation.

## 2. Materials and methods

### 2.1. MRI data acquisition

This HIPAA-compliant study was approved by the local institutional review board. Fifteen subjects (9 male, 6 female; age range 24–73) were recruited: 7 were healthy volunteers without a history of chronic illness while the other 8 had suspected liver cirrhosis (with glomerular filtration rate estimates from the serum-creatinine MDRD formula ranging from 46 to 93 ml/min). After giving written informed consent, each subject underwent renal ASL and DCE MRI scans in a 3T scanner (TimTrio; Siemens Medical Solutions, Erlangen, Germany).

For ASL imaging, we used a FAIR tagging scheme with balanced steady-state free precession (bSSFP) readout [21] with the following imaging parameter values: repetition time (TR) 3.68 ms, echo time (TE) 1.84 ms, field of view (FOV) 380 × 380 mm, matrix 256 × 256, slice thickness 8 mm, and GRAPPA acceleration factor of 2. Before recording the bSSFP signals, an alpha/2 pre-pulse and 10 dummy pulses were applied to establish a steady state. To allow for magnetization recovery after image acquisition, an idle period was appended so that the total time for each acquisition was 6 s. During a 24-s breath-hold, we were able to acquire two pairs of SS and NS images from an oblique-coronal slice through the long axis of both kidneys. For the 7 healthy volunteers, the acquisition was repeated using 16 different TIs (requiring 16 breath-holds): 150 ms, then 200 to 1600 ms at 100-ms intervals. Our preliminary study indicated that this protocol of sixteen 24-s breath-holds was challenging for diseased patients. Therefore, for the 8 cirrhosis patients included in our study, we only acquired ASL data at 5 TIs: 150, 500, 800, 1000 and 1500 ms.

Following the ASL examination, DCE MRI was performed using a previously published protocol [9,22] to obtain reference measurements of renal perfusion. Briefly, dynamic images of 2D slices through the abdominal aorta and the kidneys were acquired using a saturation-recovery-prepared FLASH sequence after the injection of 4 ml gadoteridol (500 mmol/l). The imaging slice though the kidneys was positioned to match the slice from the ASL acquisitions. This 2D sequence allowed for a high temporal resolution of 1.5 s which was important for tracking rapid tracer kinetics during the dynamic scan. Dynamic MR signals were sampled from manually drawn ROIs covering the renal cortex and medulla [23] and were then converted to the concentration of contrast material [9,24]. The volumes of the renal cortex and medulla were obtained from 3D-VIBE measurements. Using the renal volumes and an arterial input function (AIF) sampled from the abdominal aorta at the level of the renal arteries, contrast enhancement in the renal cortex and medulla was analyzed using a 3-compartment tracer kinetic model to extract renal cortical and medullary RPF. More details can be found in the published studies [9,22].

### 2.2. Quantifying renal perfusion from ASL images

The ASL images with different TIs were acquired during separate breath-holds, so there was typically some relative displacement between image sets. Therefore, the first processing step was image registration using a previously validated technique [23,25] that uses the generalized Hough transform to align all image frames with a common user-defined template. On the registered images, ROIs were defined to include all cortical regions and all medullary regions for each kidney. When defining each ROI, the renal hilum was avoided in order to exclude the segmental arteries. From the cortical and medullary ROIs for each kidney, we obtained averaged NS and SS signal values at the different TIs.

Cortical and medullary RPF was estimated from the ASL signal vs. TI curves using a tracer kinetic approach (presented in the Appendix). Briefly, we reconstructed the NS curve to correct for differences in inversion efficiency between the NS and SS inversions. A piecewise linear formula was derived to quantify the relationship between tissue perfusion and the ASL difference signals, and by fitting the formula to the signals, renal perfusion was estimated. Multiplying perfusion estimates by the cortical and medullary volumes obtained from the VIBE data yielded cortical and medullary RPF.

### 2.3. Comparing RPF between ASL and DCE MRI

The agreement between RPF measured from ASL and that from DCE MRI was evaluated by computing the mean and standard deviation of the absolute difference between the two groups of RPF values. We also computed Pearson's correlation coefficient (R) between the two groups of measurements.

Using the acquired data, we also investigated the impact of TI sampling density (analogous to temporal resolution in DCE MRI) on the accuracy of the perfusion estimates. Specifically, we down-sampled the signal vs. TI curves from the 16-TI acquisition group (Table 1). At each down-sampling step, we dropped the signals from two TI values such that the remaining TI values were as evenly distributed as possible. Perfusion values were estimated from all down-sampled signal vs. TI curves using the proposed method, and were compared to the reference values measured from DCE MRI.

## 3. Results

ASL images were acquired from all subjects without noticeable artifacts. Representative NS and SS images are shown in Fig. 1. Fig. 2 demonstrates how the proposed method was implemented for quantifying renal perfusion. In Fig. 2a, a large difference between representative NS and SS signals from the renal cortex can be observed, likely due to different NS and SS inversion efficiencies. After correcting for this discrepancy, the ASL difference signal exhibits a linear increase from which tissue perfusion can be extracted (Fig. 2b).

For the seven subjects with ASL data acquired at 16 TIs, the measured RPF was 151 ± 37 ml/min in the cortex and 25 ± 22 ml/min in the medulla. These values differ from the DCE-measured values (cortex: 152 ± 41; medulla: 43 ± 12) by 9 ± 30 ml/min. The correlation coefficient between the two groups was 0.92. For the eight subjects with ASL data acquired at 5 TIs, ASL-measured RPF was 158 ± 103 ml/min in the cortex and 36 ± 31 ml/min in the medulla, differing from the DCE-measured values (cortex: 180 ± 70; medulla: 33 ± 10) by 9 ± 57 ml/min. The correlation coefficient between the two groups was 0.81. Correlation plots for these comparisons are shown in Fig. 3.

The ASL signal vs. TI curves with 16 TIs were down-sampled, and the estimated RPF values were compared to those from DCE MRI (Table 1). As a general pattern, correlation between ASL- and DCE-measured RPF values decreased with TI-sampling density, from