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CLINICAL RESEARCH

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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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 acquisitions[13] 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 sequence[13] 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 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] Q2 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 Q3 following each 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 FISP sequence (TR/TE = 4.0/2.02 milliseconds; Q4 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 FLASH readout (TR/TE = 2.2/1.2 ms; FA = 5°; field of view = 400 × 400 mm^2; matrix = 96 × 96; BW = 1000 Hz/pixel; 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