Angiotensin-converting enzyme inhibitor-enhanced MR renography: repeated measures of GFR and RPF in hypertensive patients

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Submitted 29 October 2008; accepted in final form 20 January 2009

Zhang JL, Rusinek H, Bokacheva L, Lim RP, Chen Q, Storey P, Prince K, Hecht EM, Kim DC, Lee VS. Angiotensin-converting enzyme inhibitor-enhanced MR renography: repeated measures of GFR and RPF in hypertensive patients. Am J Physiol Renal Physiol 296: F884–F891, 2009. First published January 21, 2009; doi:10.1152/ajprenal.90648.2008.—This study aims to assess the feasibility of a protocol to diagnose renovascular disease using dual MR renography acquisitions: before and after administration of angiotensin-converting enzyme inhibitor (ACEi). Results of our simulation study aimed at testing the reproducibility of glomerular filtration rate (GFR) and renal plasma flow demonstrate that for a fixed overall dose of 12 ml gadolinium-based contrast material (500 mmol/l), the second dose should be approximately twice as large as the first dose. A three-compartment model for analyzing the second-injection data was shown to appropriately handle the tracer residue from the first injection. The optimized protocol was applied to 18 hypertensive patients without renovascular disease, showing minimal systematic difference in GFR measurements before and after ACEi of 0.8 ± 4.4 ml/min or 2.7 ± 14.9%. For 10 kidneys with significant renal artery stenosis, GFR decreased significantly after ACEi (P < 0.001, T value = 3.79), and the difference in GFR measurements before and after ACEi averaged 8.3 ± 6.9 ml/min or 26.2 ± 43.9%. Dual-injection MRI with optimized dose distribution appears promising for ACEi renography by offering measures of GFR changes with clinically acceptable precision and accuracy.

Dynamic contrast-enhanced MRI is an alternative diagnostic procedure that allows a comprehensive exam of both renal vascular disease with MR angiography (MRA) and renal function with MR renography (MRR) in a single session (19). The commonly used tracer Gd-based contrast agent (gadopentetate dimeglumine or gadoteridol) is freely filtered at the glomerulus and does not experience reabsorption or secretion along tubules. With appropriate image segmentation (20) and tracer kinetic modeling (2, 6, 8, 12, 30), multiple parameters associated with perfusion, filtration, and tubular function can be identified. Using MRR in a swine model, Prasad et al. (19) demonstrated delay in tracer washout (due to reduced GFR) after the administration of captopril in kidneys with significant RAS.

This study investigates the feasibility of a single examination in which baseline and post-ACEi MRR are performed in quick succession, followed by contrast-enhanced MRA. To diagnose RVD and predict response to therapy, the goal is to measure single-kidney GFR before and after the ACEi with sufficient precision that changes in GFR in the presence of RVD can be detected. The overall dose of the injected tracer is limited because of the risk of nephrogenic systemic fibrosis (NSF) and the nonlinear and nonmonotonic relationship between Gd contrast concentration and signal intensity, where at high concentrations, signal loss may occur due to transverse relaxation time (T2) effects. Therefore, we sought to determine, for a given total Gd chelate dose, the optimal distribution of that dose across two injections (d1 and d2). Our outcome measure is the precision of measured changes in renal function between the two injections.

In the first part of this paper, we use simulation techniques to evaluate the precision of two consecutive RPF and two GFR measurements and their changes using MRR. We also analyze the effects of the presence of residual tracer from the first injection on the post-ACEi results. A conventional “back-
ground subtraction” method is used where the residual is subtracted from the second-injection data to reset baseline for the second MRR concentration curves to zero. As an alternative to this approach, we present a procedure based on modeling the residual concentration from the first injection in the analysis of the second injection and demonstrate reduced error for the new procedure. Furthermore, to validate our simulations, we report the initial results from a clinical dual-injection MRR study. We studied hypertensive subjects referred for evaluation of RAS. In those without RAS, we hypothesized that the ACEi should have minimal effect on renal function, and therefore used changes in GFR and RPF measurements obtained pre- and post-ACEi as an estimate of reproducibility (precision) in dual-injection MRR. We also compared repeat measurements of GFR in these patients with the values obtained in a subset of patients with significant RAS. Since prior work established that significant RAS is associated with a decrease in GFR after ACEi (3, 19), to validate dual-injection MRR we tested the sensitivity of GFR decrease in separating the kidneys with significant RAS from those without RAS.

**MATERIALS AND METHODS**

**MRR Technique**

All Monte Carlo simulations and clinical examinations using MRR were based on a standard MR protocol performed on a 1.5 T MR system using a body phased array coil. Serial coronal three-dimensional (3D) spoiled gradient recalled echo (GRE) images were acquired at 1.5 T (Avanto, Siemens Medical Solutions, Erlangen, Germany) using the following parameters: TR/TE/flip angle = 2.84 ms/1.05 ms/12°, partition matrix 161 × 256 × 20 interpolated to 256 × 256 × 40, field of view 400 × 400 × 100 mm, voxel size 1.6 × 1.6 × 2.5 mm, parallel imaging acceleration factor of 3, acquisition time 3 s. Before contrast administration, five 3D images were acquired during one 15-s breath-hold, to obtain a reliable precontrast signal for measurement of tracer concentration. A bolus injection of 4 ml Gd-based contrast agent was intravenously administered, followed by a 20-ml saline flush at 2 ml/s (Simulation Studies explains how we arrived at the dose distribution). Eight seconds following the start of Gd-DTPA injection, 10 3D acquisitions were repeated continuously for 30 s, during which time the subject was asked to suspend respiration for as long as possible. Sixteen additional 3D images were acquired during separate 3-s breath-holds for ~10 min thereafter.

About 3 min before the end of the first MRR acquisition, an ACEi enalaprilat (0.04 mg/kg, up to 2.5 mg) was administered intravenously over 3 min. Typically, 7–10 min after the baseline scan ended, the post-ACEi scan started. For the post-ACEi scan, an 8-ml bolus of Gd-based contrast agent was injected. The MRR imaging protocol was the same as for the baseline scan.

Semiautomated image registration and segmentation of the 3D MRR data sets were performed to produce aortic, renal cortical, and renal medullary signal intensity vs. time curves (20). These signal curves were converted to concentration vs. time curves for the renal cortex and renal medulla and aorta, as previously reported (1). Briefly, the relationship between T1 and signal intensity (SI) for the gradient echo MRR sequence is expressed as

\[ SI = g \cdot f(T_1) \]  

(1)

where g is a scaling term that depends on a variety of factors, such as subject habitus, system gain, and coil sensitivity, and \( f(T_1) \) is a function that depends only on sequence parameters. Function f can be derived analytically or empirically by phantom experiments (1). With known f, g can be determined for each region (aorta, cortex, and medulla) using precontrast T1 value (T10). For any contrast-enhanced SI value from dynamic images, the corresponding postcontrast T1 value can be estimated using equation 1. The concentration ([Gd]) of the tracer that induces the change in T1 value can be further estimated as

\[ [\text{Gd}] = \left( \frac{1/T_1 - 1/T_1^0}{r_1} \right) \]

(2)

where \( r_1 \) is the relaxivity of gadolinium contrast (4.5 mM⁻¹ s⁻¹). For conversions in the simulations, T1 values for aorta, renal cortex, and medulla were set at 1,200, 880, and 1,160 ms, respectively, and g at 2,800. All values are typical for our patient cases and MR system.

For patient study, the converted concentration vs. time curve for aorta, termed AIF, may be problematic due to several MR artifacts such as inflow effect. We normalized the AIF for the second injection assuming that patient’s cardiac output Q remains constant throughout the exam. The procedure consists of two steps: 1) estimate Q with the first dose \( d_1 \) and the AIF for the first injection, based on the dye dilution principle (16); and 2) scale the AIF for the second injection using the estimated Q and the known dose \( d_2 \).

The concentration curves were subjected to the parameter-fitting procedure described below to derive renal functional parameters such as RPF and GFR.

**Analysis of Renal Function using Tracer Kinetic Model**

A previously validated three-compartment model was used for data analysis (12, 30). Briefly, from the abdominal aorta (Ao) the tracer transits through renal vascular pathway (A, arterioles and vasa recta), tubules (P), and loops of Henle (L; Fig. 1). RPF represents the flow into compartment A, and GFR the flow from A to P. Compartment A is distributed in both renal cortex and medulla, compartment P in renal cortex, and L in medulla. Hence, tracer retention curves of renal cortex and medulla (MCx and MMed) can be expressed as

\[
\begin{align*}
M_{Cx} &= w_{A,Cx}M_A + M_p \\
M_{Med} &= (1 - w_{A,Cx})M_A + M_L
\end{align*}
\]

(3)

where \( w_{A,Cx} \) is the volume fraction of A in renal cortex, and \( M_A, M_P, \) and \( M_L \) are the compartmental retentions.

The dynamics of tracer propagation in each compartment are characterized by the compartmental impulse retention function \( R(t) \). This function depicts tracer retention following an idealized scenario of a direct application of a unit impulse, i.e., the instantaneous bolus injection of unit dose of tracer. Given Ao, the aortic input function measured in units of tracer concentration, the tracer retention in the A compartment, \( M_A \), is (30)

\[ M_A = \frac{RPF}{1 - Hct} \cdot \frac{Ao \otimes R_A}{A} \]

(4)

where Hct is the hematocrit, \( R_A \) is the tracer retention in the vascular compartment, and \( \otimes \) denotes convolution.

To compute retention in P and L compartments based on the input function Ao, we need to know the retention function \( R(t) \) that reflects the indirect (distal) tracer input. In a previous paper (30), we showed how to derive \( R(t) \) for P and L compartments. Using these derivations, we have

\[
\begin{align*}
&\text{Ao} & \text{RPF} \\
& A & GFR \\
& P & L
\end{align*}
\]

Fig. 1. Schematic diagram of 3-compartment model. A, intrarenal arteriages; P, proximal tubule; L, loop of Henle. Renal plasma flow (RPF) represents the flow rate into A, and glomerular filtration rate (GFR) the flow rate from A to P. Solid arrow denotes tracer flow, and dashed arrow denotes water reabsorption.
We can express the regional tracer retentions (M_{Ca} and M_{Med}) by aortic input (Ao) and the model parameters including GFR, RPF, mean transit times, and washout rates for each of the three compartments (A, P, L) (30). The model parameters can be identified by minimizing the residual discrepancy (root mean square difference) between the measured retentions (M_{Ca} and M_{Med}) and the model-constructed ones. This is implemented using the iterative Levenberg-Marquardt minimization algorithm (13). We previously showed that GFR and RPF have sufficient sensitivity to measured data as to be reliably identified by the three-compartmental renal model (12, 30). We also showed that 3D image segmentation of MRR data into renal cortex and renal medulla is relatively accurate and segmented curves provide valid measure of renal function by this model (20).

### Analysis of post-ACEi MRR: Residual Tracer from pre-ACEi Injection

The biological half-life of Gd-DTPA in the kidney is ~1–2 h and even longer for patients with renal dysfunction. In double-injection MRR, residual tracer from the baseline scan is present in the kidney at the time the second dose of tracer (for the post-ACEi scan) is injected. We examined two methods for accounting for residual tracer in the analysis of the post-ACEi scan: the baseline subtraction method and a model-derived initial value method.

**Baseline subtraction method.** In the conventional method (25), residual Gd tracer in renal cortex and medulla from the end of the first MRR study (pre-ACEi) is subtracted from the cortical and the medullary curves for the second-injection data. Resulting curves for post-ACEi data have zero Gd retentions at the start of the second injection and are fitted with the same model as for the first-injection data.

**Model-derived initial value method.** For the alternative method, the analysis of the post-ACEi data considers separately the tracer kinetics of the contrast material in each injection. The residual contrast from the first injection is taken as the initial value for the second injection, and modeled as an impulse input presented directly into the compartment. This impulse input transits through the originating compartment and then through the subsequent ones (Fig. 1). Take compartment P as an example. Tracer retention in P during the second MRR study is the impulse at P compartment.

\[
M_{P1} = \frac{RPF}{1 - Hct} Ao \otimes R_{P1}, \quad M_{L1} = \frac{RPF}{1 - Hct} Ao \otimes R_{L1}
\]

(5)

The tracer residues from first injection, denoted as M_{A1} (i = A, P, or L), can be estimated by sampling compartmental curves just before the start time of the post-ACEi scan. R_{P2,L2} represents the tracer retention in L compartment as a function of time, induced by unit impulse at P compartment. \(\delta\) is a unit impulse function.

Substituting the compartmental retentions shown in equation 6 into equation 3 gives the three-compartment model used in fitting the second-injection data. As in fitting of the baseline curves, functional parameters RPF_2, GFR_2, etc. are obtained by minimizing the residual discrepancy between the model-constructed retentions and the measured ones.

### Simulation Studies

Our analysis of dual-injection MRR assumes that the total tracer dose \(d_0\) is given. Using simulation techniques, we investigate different sub-divisions of \(d_0\) into the first-injection dose \(d_1\) and the second dose \(d_2\) (= \(d_0 - d_1\)), where each injection is performed under the same physiologic conditions so that we expect GFR_1 = GFR_2 and RPF_1 = RPF_2. We fix \(d_0 = 12\) ml Gd-DTPA (with standard concentration of 500 mmol/l). We assume that the measurements of kidney function (such as GFR or RPF) are the main diagnostic interest and assess differences in estimates based on two separate injections, using doses \(d_1\) and \(d_2\). Our simulations vary the distribution \(d_1\) and \(d_2\); the precision of GFR_2 – GFR_1 and that of RPF_2 – RPF_1 are taken as the main outcome.

We began by generating a representative and low-noise arterial input function \(A_0(t)\), for a single injection. \(A_0\) was obtained by averaging arterial concentrations in 24 subjects, after aligning the time axis to match the time of arterial peaks. The concentrations were derived from single-injection 10-min exams. \(A_0\) was extrapolated to 30 min by assuming a biexponential behavior of the arterial concentration curve beyond 5 min. A representative arterial input in a dual-injection experiment was simulated as

\[
A(t) = (d_1d_2)A_0(t) + (d_1d_3)A_0(t - \tau)
\]

(7)

where \(\tau\) is the time delay between the two injections. In all experiments below we assume \(\tau\) of 20 min, which is sufficient to administer ACEi challenge.

Tracer concentration vs. time curves for renal cortex and medulla were then constructed by convolving \(A(t)\) with impulse retention functions based on equations 3–5. The temporal resolution of MRR was assumed equal to 3 s/frame. Since each MRR exam extends over 10 min, with a 10-min delay between them, the total simulation time for the simulated dual-injection experiment was 30 min. For addition of noise, we converted the concentrations (aorta, cortex, and medulla) to signal intensities, and added random noise (1). The level of noise was chosen to be 5% of precontrast cortical signal intensity. The noisy signal intensity vs. time curves were converted to concentration vs. time curves as described in MRR Technique.

The concentration vs. time curves for aorta, cortex, and medulla were separated into the first data set (the first 10 min) and the postchallenge data set (the last 10 min). Both data sets were then subjected to the parameter-fitting procedure. The Monte-Carlo process of adding random data noise was repeated \(n_{\text{trials}}\) times. The value of \(n_{\text{trials}}\) was determined by analyzing the convergence rate of observed standard deviations of all relevant functional parameters provided by the model. In all scenarios, \(n_{\text{trials}} = 1,000\) was sufficient for ±3% accuracy.

For each simulation scenario, we assume no RVD so that GFR_1 = GFR_2. Two scenarios were considered, reflecting different functional status for the kidney: 1) normal where GFR_1 = GFR_2 = 58 ml/min, RPF_1 = RPF_2 = 168 ml/min and 2) dysfunctional where GFR_1 = GFR_2 = 24 ml/min, RPF_1 = RPF_2 = 76 ml/min. In the simulation, five combinations of \(d_1\) and \(d_2\) (\(2 + 10, 4 + 8, 6 + 6, 8 + 4, 10 + 2\) ml) were compared for each scenario. The mean and SD for these four parameters (GFR_1, GFR_2, RPF_1, and RPF_2) and their differences, GFR_2 – GFR_1 and RPF_2 – RPF_1 were calculated over \(n_{\text{trials}}\) simulations. The SD indicates the precision of the parameters, and the deviation of the mean value from the value assumed in simulation experiments indicates the measurement bias. The optimal dose distribution should result in high precision and low bias for GFR_2 – GFR_1 and RPF_2 – RPF_1.

To compare the conventional background subtraction method with the initial value method for addressing residual gadolinium from the first injection at the time of the second injection, data from Monte Carlo trials were processed with both methods. This analysis focused on comparing the deviation of parameters GFR_2 and RPF_2 from their true value. Deviations obtained with the conventional and initial value...
were taken as a reflection of the reproducibility or reliability of our measurement technique and were compared using paired t-test, Pearson’s correlation coefficient, and a Bland-Altman plot. SD of the changes in each parameter (e.g., GFR2 – GFR1) across the nonstenotic kidneys was calculated as a measure of the reproducibility of the proposed method. For the stenotic kidneys in group B, correlation coefficient and linear regression were used to evaluate the possible change in GFR and RPF due to ACEi. We also tested the sensitivity and the specificity of relative or percentage GFR decrease, i.e., (GFR2 – GFR3)/GFR1, in discriminating nonstenotic and significantly stenotic kidneys.

RESULTS

Simulations

Figure 2 plots the distribution of GFR2 – GFR1 and RPF2 – RPF1. As the dose for the first injection (d1) increased from 2 to 10 ml, the SD of GFR2 – GFR1 (reflecting its precision) first decreased then increased, for both the normal and the dysfunctional kidney scenarios. The minimum SD occurs for d1 = 4 ml and d2 = 8 ml. The same behavior of SD is observed for RPF (Fig. 2B). At d1 = 4 ml and d2 = 8 ml, GFR2 – GFR1 has comparable and minimal bias, <1 ml/min for both normal and dysfunctional cases. The biases for RPF2 – RPF1 at d1 = 4 ml are about half of those at d1 = 6 ml. Overall, the optimal dose distribution appears to be d1 = 4 ml and d2 = 8 ml.

Figure 3 compares two methods of correcting for the residual tracer from the first MRR injection when analyzing second MRR acquisition data. With the initial value method, the systematic error in GFR2 is less than 8% across all dose distributions (Fig. 3, A and B). The conventional subtraction method underestimates GFR2 by an amount that progressively increases as d1 increases, reaching an error larger than 60% for d1 of 10 ml (Fig. 3, A and B). At d1 of 4 ml, the accuracy of GFR2 estimates by the proposed method is significantly better than that by the conventional method (P < 0.001).

For both the conventional subtraction and proposed initial value methods, the systematic error in RPF2 estimates increases as d1 increases (Fig. 3, C and D). At every dose distribution, this systematic error by the proposed method is roughly half that by the conventional method. At the optimal dose distribution of d1 = 4 ml and d2 = 8 ml, the accuracy of RPF2 estimates by the proposed method is significantly better than that by the conventional method (P < 0.001).

Patient Study

Tracer retention curves from a representative kidney, together with the model fits, are shown in Fig. 4. Two MRR acquisitions were performed, first using d1 = 4 ml and the second, starting 10 min after the conclusion of the first, using d2 = 8 ml. For both cortex and medulla, the retention curves from the second-injection data are higher than those from the first injection because of the residual contrast from the first injection as well as because of the larger dose used for the second injection (8 vs. 4 ml). Tracer residues in both renal cortex and medulla are little changed between the tail of the first injection (10 min) and the beginning (before) of the second injection (20 min). With the residues appropriately handled by the initial value model (equation 6), the cortical and medullary concentration vs. time curves from the second MRR acquisition were well fitted, with relative root mean square (RMS) error 7.0% for cortex and 8.0% for medulla.
American Journal of Physiology—Renal Physiology

Assessment of Renal Function by Dual-Injection MRI

Fig. 2. Monte Carlo simulated estimates of renal function expressed as differences in renal function between first and second MR renography (MRR) acquisitions using \(d_1\) for the first injection and assuming a total dose of 12 ml (\(d_2 = 12\) ml – \(d_1\)). Plots show the simulated changes in renal function: GFR\(_2\) – GFR\(_1\) (A) and RPF\(_2\) – RPF\(_1\) (B) for each combination of doses and for 2 scenarios, a normally functioning kidney and a dysfunctional kidney. In this simulation, the true values of GFR\(_2\) – GFR\(_1\) and RPF\(_2\) – RPF\(_1\) are 0. Error bars denote mean value ± SD.

In total, 43 kidneys from 26 subjects were examined using the dual-injection protocol and curve fitting for the first MRR acquisition resulted in relative RMS averages of 11.8 ± 4.0% for cortex and 13.1 ± 5.0% for medulla. For second MRR acquisitions, the fits were better, with relative RMS errors averaging 6.8 ± 2.2% for cortex and 7.5 ± 2.9% for medulla. Total GFR by our MR approach correlated moderately with eGFR from MDRD formula (\(r = 0.522, P = 0.011\); Fig. 5).

Derived in baseline MRR without ACEI, RPF\(_1\) estimates for the 33 kidneys without RAS in group A were significantly higher than those for the 10 kidneys with significant RAS in group B (Table 2). Similarly, GFR\(_1\) estimates for the non-RAS kidneys were significantly higher than those for the RAS kidneys, but the difference was not as large as that in RPF (Table 2).

In the 33 kidneys without RAS (group A), GFR\(_1\) estimates correlated well with GFR\(_2\) estimates (Fig. 6A; regression equation GFR\(_2\) = 1.00 GFR\(_1\) – 0.77 and correlation coefficient 0.931). Bland-Altman plot shows that the differences GFR\(_2\) – GFR\(_1\) averaged −0.8 ± 4.4 ml/min (or −2.7 ± 14.9% of GFR\(_1\)) with 95% confidence interval between −9.3 and 7.8 ml/min (Fig. 6B). Paired t-test indicated no significant difference between the two estimates (paired t-test, \(T = 0.99, P = 0.33\)). In contrast, GFR\(_2\) estimates for the 10 kidneys of significant RAS in group B were significantly lower than GFR\(_1\) (paired t-test, \(T = 3.79, P = 0.004\)), and regression equation was GFR\(_2\) = 0.52 GFR\(_1\) + 1.67 (Fig. 6A). The difference GFR\(_2\) – GFR\(_1\) averaged −8.3 ± 6.9 ml/min (or −26.2 ± 43.9% of GFR\(_1\)). A cutoff value of 27.6% for (GFR\(_2\) – GFR\(_1\))/GFR\(_1\) resulted in 80% sensitivity and 94% specificity for detecting significant RAS.

RPF estimates of the nonstenotic patients in group A show a correlation coefficient 0.870 before and after ACEI (Fig. 7A; regression equation, RPF\(_2\) = 0.75 RPF\(_1\) + 47.5). Differences between the two RPF estimates (RPF\(_2\) – RPF\(_1\)) averaged 9.2 ± 34.6 ml/min (or 13.6 ± 28.7% of RPF\(_1\)) with 95% confidence interval between −58.6 and 76.9 ml/min (Fig. 7B). No significant difference was observed between RPF\(_1\) and RPF\(_2\) (paired t-test, \(T = 1.52, P = 0.14\)). Similarly for the kidneys with significant RAS in group B, there was no significant difference between RPF\(_1\) and RPF\(_2\) (paired t-test, \(T = 1.1, P = 0.30\)). Regression equation for RPF\(_1\) and RPF\(_2\) was RPF\(_2\) = 0.50 RPF\(_1\) + 26.3. The difference RPF\(_2\) – RPF\(_1\) averaged −8.0 ± 23.1 ml/min (or −0.50 ± 34.7% of RPF\(_1\)).

DISCUSSION

ACEI-enhanced MRR offers the opportunity to improve the diagnosis of RVD by providing functional information to complement vascular imaging using MRA. MRR can be performed before and after an ACEI and changes in GFR can be used to diagnose RVD. According to a previous consensus report (25), a decrease in GFR larger than 10% (for example, a decrease of 6 ml/min for GFR 60 ml/min) after ACEI indicates high probability of RVH. In our study, we sought to determine the optimal dose distribution for pre- and post-ACEI MRR protocols and to analyze precision and accuracy in measuring GFR and RPF before and after ACEI. We also tested this protocol in a small sample of subjects referred for evaluation of RVD.

Our simulations show that approximately twice as large a dose should be given for the second injection than for the first injection. In our simulation and patient protocol, the time interval between the start of the two injections was set at 20 min to keep the MRR portion of study within 30 min. Hence, a significant amount of tracer from the baseline study was retained in the kidney at the time of the second injection. We found that a larger dose given in the second study helps minimize the relative effect of the residue, thereby balancing the precision of the serial parameter estimates of GFR\(_1\) and GFR\(_2\). Balancing the precision appears to maximize the precision of the difference measure GFR\(_2\) – GFR\(_1\).

One challenge in analyzing dual-injection data is the handling of the residual contrast material in the kidney at the time of the second injection. During the second scan, the residue diminishes due to continuous excretion of the kidney. However, using the conventional background subtraction method, residues are assumed constant during the second scan. The simulations revealed a significant artifactual bias associated with background subtraction. At optimal dose distribution (\(d_1 = 4\) ml, \(d_2 = 8\) ml) the second GFR is systematically underestimated by 7.4–8.9% (8.9 ± 8.6% for the normal kidney and 7.4 ± 15% for the dysfunctional one). Given that a threshold...
of ~10% decrease in GFR may be used to diagnose RVD, this underestimation may possibly lead to false positives or misdiagnoses. Using our initial value method for analyzing the second-injection data, our simulations predicted negligible ~1% (0.7 ± 8% for normal and 1.2 ± 14.8% for dysfunctional kidney) systematic error in GFR2. The magnitude of the residue during the second scan depends on the filtration rate and is different for the normal and the dysfunctional kidneys. However, for the simulated normal and dysfunctional kidneys, the errors in GFR2 were comparable (0.4 ± 4.6 vs. 0.3 ± 3.5 ml/min), supporting the validity of the proposed method.

In our patient study, tGFR derived by MRR (baseline values before ACEi) correlated only moderately with the eGFR by the formula of MDRD (r = 0.522). This may be due to the fact that serum creatinine level does not reliably reflect renal function in elderly patients (23).

Our study of patients without RAS (group A) confirmed good agreement between GFR1 and GFR2, with correlation coefficient of 0.931 and GFR2 = GFR1 averaging −0.8 ± 4.4 ml/min or 2.7 ± 14.9% of GFR1. These results are promising.

Fig. 3. Monte Carlo simulated estimates of renal function parameters (mean ± SD) for the second of 2 MRR acquisitions. A and B: GFR2 of the normal and the dysfunctional kidneys. C and D: RPF2 of the normal and the dysfunctional kidney. Two methods of correcting tracer residue from the first injection are tested: conventional background subtraction method (shown as squares) and initial value method described by equation 6 (circles). Results show consistently lower bias using the initial value method. Dashed lines are true values for the parameters in the simulation. At dose distribution (d1, d2) of 4 and 8 ml, the proposed initial value method reduces measurement bias while preserving the precision of GFR and RPF.

Fig. 4. Measured double-injection MRR data and model fits for a representative kidney: A: tracer concentrations measured from an aortic region of interest. B: tracer retention in cortex is represented by squares and that from medulla by circles. The first-injection data (0–10 min) were fitted using the model described by equations 3–5 (solid lines), with results GFR1 = 43.8 ml/min, RPF1 = 208.4 ml/min. The second-injection data (20–30 min) were fitted using the model described in equations 3 and 6 (dashed lines), with results GFR2 = 44.9 ml/min, RPF2 = 177.6 ml/min. In this case, GFR2 − GFR1 = 1.1 ml/min, while RPF2 − RPF1 = −30.8 ml/min. In the absence of renovascular disease, the expected GFR2 − GFR1 value is 0.

Fig. 5. Correlation of estimated GFR (eGFR by MDRD) and total GFR (GFR; sum of the single-kidney GFRs by MRR). Regression equation is tGFR = 0.37 eGFR + 31.2, and correlation coefficient r = 0.522 (P = 0.011). Solid line is identity line and dashed line is regression line.
for the application of this technique to the diagnosis of RVD. For one preliminary group of kidneys with RAS (≥50%), a significant decrease in GFR was observed after ACEi, with GFR2 averaging 8.3 ml/min (or 26.2 ± 43.9% of GFR1).

Based on current study, the estimated SD of the difference GFR2 - GFR1 in the nonstenotic kidneys is 4.4 ml/min. Assuming that ACEi had no physiologic effect in these kidneys, the relative reproducibility of GFR change was 14.9% of GFR1 (multiple patients in this study had low GFR1). This level of precision compares favorably with plasma clearance methods in nuclear medicine. Using multiple sample method, Piepsz et al. (18) measured a precision of 9.0 ml/min 1.73 m² for 51Cr-EDTA clearance, and a precision of 53.7 ml·min⁻¹·1.73 m² for ⁹⁹mTc-MAG3 clearance. Clearly, the precision of these clearance measurements would be worse for single kidneys.

Both simulations and the patient study suggest relatively poor reproducibility of RPF, with coefficient of variability in the 15–20% range. Several explanations for this can be proposed: invalid treatment of vascular pool in the three-compartmental model, insufficient temporal resolution to measure RPF with accuracy, and random errors in arterial input function. In addition, the variability in RPF could be possibly due to the short-term (cycle length ~40 s) oscillation in renal blood flow in patients with essential hypertension, as suggested by previous studies (9, 10). While resolution of this issue will require further work, it should be noted that GFR measures may be clinically more relevant than measurements of perfusion.

The study has several limitations. First, the simulation study only simulated random noise (thermal MRI noise). In reality, the data are contaminated with physiological noise (e.g., patient motion). Nevertheless, we found good agreement between simulations and patient estimates of precision. Second, in our patient study, we had so far only eight subjects with RAS. More cases are needed for validating the proposed method.

Gadolinium-based contrast agents, especially gadodiamide (Gd-DTPA-BMA) and to a lesser extent gadopentetate dimeglumine (Gd-DTPA), may cause NSF in patients with renal...
insufficiency, and the risk of NSF seems to be dose dependent (5, 22, 27). In our study, we used low dose of Gd-DTPA (12 ml for both injections combined). Even with Gd-MRA using a single dose, the total dose is <0.2 mmol/kg. No NSF symptom has been reported for our patients. To minimize the risk of NSF, our new protocol uses gadoteridol (Gd-Hp-D03A). Based on current data, Gd-Hp-D03A is considered to be significantly safer than Gd-DTPA because of its stable macrocyclic structure (22).

In summary, dual-injection MRR with optimized dose distribution appears promising for ACEi renography by offering reliable and reproducible measures of GFR, with acceptable precision and accuracy. Studies to validate our dual MRR approach as a diagnostic tool for RVD in conjunction with renal MRA are underway.

GRANTS
This work was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases Grants DK-063183 and DK-061599.

REFERENCES