Angiotensin-Converting Enzyme Inhibitor-Enhanced MR Renography: Repeated Measures of GFR and RPF in Hypertensive Patients

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Abstract

This study aims to assess the feasibility of a protocol to diagnose renovascular disease using dual MR renography (MRR) 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 (RPF) 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.

Key words: angiotensin converting enzyme inhibitor, glomerular filtration rate, renovascular disease, compartmental modeling
Renovascular disease (RVD) is the most common curable form of hypertension and renal insufficiency in humans. Of the 60 million Americans estimated to have hypertension, approximately 1-5% have RVD. For the diagnosis of RVD, renal scintigraphy is typically performed following an angiotensin-converting enzyme-inhibitor (ACEi) such as captopril. In kidneys with significant renal artery stenosis, glomerular filtration rate (GFR) is often preserved because activation of the renin-angiotensin system leads to efferent arteriolar vasoconstriction and increased pressure at the glomerulus. The ACEi reverses efferent arteriolar vasoconstriction and leads to a decrease in GFR. GFR reduction of more than 10% indicates high probability of renovascular hypertension (RVH) (25, 26, 29). The ACEi-induced change in renal perfusion such as renal plasma flow (RPF) could serve a complementary role (25), although the significance of change in RPF due to ACEi as measured in renal scintigraphy is controversial (7, 17, 21, 29). Such protocol has been proposed as a predictor of successful revascularization among patients with renal artery stenosis as the cause of hypertension (4, 7, 11, 15, 21, 25, 26, 28, 29).

The protocol for dual-injection scintigraphy using Tc$^{99m}$-MAG3 or Tc$^{99m}$-DTPA pre- and post-ACEi has been extensively studied (25, 26). When performed on the same day, standard protocol calls for the 2nd dose of radioactive tracer to be 5-10 times larger than the first one (1 mCi vs 5-10 mCi) (24-26) and for a 40-60 min delay between the 1st and the 2nd injection to minimize the residual activity from the baseline scan (25). Alternatively, the two scans can be performed on two separate days.
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 MR renography 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 systematic 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 $T_2$ effects. Therefore we sought to determine, for a given total Gd chelate dose, the optimal distribution of that dose across two injections ($d_1$ and $d_2$). 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 “background 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 renal artery stenosis (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 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. Prior to contrast administration, five 3D images were acquired during one 15 s breath-hold, to obtain a reliable pre-contrast 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 (The section Simulation Studies below explains how we arrived at the dose distribution). Eight seconds following the start of Gd-DTPA injection, ten 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 about 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.

Semi-automated image registration and segmentation of the 3D MRR data sets were performed to produce aortic, renal cortical, and renal medullary signal intensity versus 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 relation between $T_1$ and signal intensity (SI) for the gradient-echo MR renography sequence is expressed as

$$SI = g \cdot f(T_1),$$  \hspace{1cm} (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 pre-contrast $T_1$ value ($T_1^0$).

For any contrast-enhanced signal intensity value from dynamic images, the corresponding post-contrast $T_1$ value can be estimated using Equation (1). The concentration ([Gd]) of the tracer that induces the change in $T_1$ value can be further estimated as

$$[Gd] = \left(1/T_1 - 1/T_1^0\right)/r_1,$$  \hspace{1cm} (2)

where $r_1$ is the relaxivity of gadolinium contrast (4.5 mM\(^{-1}\cdot\text{s}^{-1})$. For conversions in the simulations, $T_1^0$ values for aorta, renal cortex and medulla were set at 1200, 880 and 1160 ms, respectively, and $g$ at 2800. All values are typical for our patient cases and MR system.

For patient study, the converted concentration versus time curve for aorta, termed AIF, may be problematic due to several MR artifacts such as inflow effect. We have 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); 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 renal plasma flow (RPF) and glomerular filtration rate (GFR).

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

A previously validated 3-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 \((L)\) (Figure 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 \((M_{Cx}\) and \(M_{Med})\) can be expressed as:

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

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 \(R_i(t)\). 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)
\[ M_A = \frac{RPF}{1 - Hct} Ao \otimes R_A \]  

(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 \( \hat{R}_i(t) \) that reflects the indirect (distal) tracer input. In a previous paper (30) we have shown how to derive \( \hat{R}_i(t) \) for \( P \) and \( L \) compartments. Using these derivations, we have:

\[ M_p = \frac{RPF}{1 - Hct} Ao \otimes \hat{R}_p, \quad M_L = \frac{RPF}{1 - Hct} Ao \otimes \hat{R}_L \]  

(5)

We can express the regional tracer retentions (\( M_{Cx} \) 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 (\( M_{Cx} \) and \( M_{Med} \)) and the model-constructed ones. This is implemented using the iterative Levenberg-Marquardt minimization algorithm (13). We have previously shown that GFR and RPF have sufficient sensitivity to measured data as to be reliably identified by the three-compartmental renal model (12, 30). We have also shown that 3D image segmentation of MRR data into renal cortex and renal medulla are 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 about 1~2 hours 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) are 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 are taken as the initial values 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 (Figure 1). Take compartment $P$ as an example. Tracer retention in $P$ during the second MRR study is the sum of tracer from three sources: aortic input ($Ao_2$), tracer residue in compartment $A$ that then transits through $P$, and residue in $P$ itself. Note that $Ao_2$ also contains the tracer residue in the aorta from the first injection. The compartmental retentions during post-ACEi scan, $M_{i2}$ ($i = A, P$ or $L$), are expressed as,
\[
\begin{align*}
M_{A2} &= \left[ \frac{RPF_2}{1-Hct} \cdot Ao_2 + M_{A1} \cdot \delta \right] \otimes \hat{R}_{A2} \\
M_{P2} &= \left[ \frac{RPF_2}{1-Hct} \cdot Ao_2 + M_{A1} \cdot \delta \right] \otimes \hat{R}_{P2} + M_{P1} \cdot \delta \otimes R_{P2} \\
M_{L2} &= \left[ \frac{RPF_2}{1-Hct} \cdot Ao_2 + M_{A1} \cdot \delta \right] \otimes \hat{R}_{L2} + M_{P1} \cdot \delta \otimes R_{PL2} + M_{L1} \cdot \delta \otimes R_{L2}
\end{align*}
\]  

The tracer residues from first injection, denoted as \( M_{i1} \) \((i = A, P \text{ or } L)\), can be estimated by sampling compartmental curves just before the start time of the post-ACEi scan. \( R_{PL2} \) 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 3-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 subdivisions 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 \( d_0 = 12 \text{ ml Gd-DTPA} \) (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-minute exams. $A_0$ was extrapolated to 30 minutes by assuming a bi-exponential behavior of the arterial concentration curve beyond 5 minutes. A representative arterial input in a dual injection experiment was simulated as

$$A(t) = (d_1/d_0)A_0(t) + (d_2/d_0)A_0(t-t_d)$$  \hspace{1cm} (7)

where $t_d$ is the time delay between the two injections. In all experiments below we assume $t_d$ of 20 minutes, 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 sec/frame. Since each MRR exam extends over 10 minutes, with a 10 min delay between them, the total acquisition time for the simulated dual-injection experiment was 30 minutes. 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 pre-contrast cortical signal intensity. The noisy signal intensity versus time curves were converted to concentration versus time curves as described in the above ‘MRR technique’ section.
The concentration versus time curves for aorta, cortex and medulla were separated into the first dataset (the first 10 mins) and the post-challenge dataset (the last 10 mins). 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: (a) normal where $GFR_1 = GFR_2 = 58 \text{ ml/min}$, $RPF_1 = RPF_2 = 168 \text{ ml/min}$ and (b) dysfunctional where $GFR_1 = GFR_2 = 24 \text{ ml/min}$, $RPF_1 = RPF_2 = 76 \text{ ml/min}$). 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 standard deviations (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 methods were compared using paired t-test. Statistical significance was assumed for $P<0.05$.

**Patient Study**

A patient study was carried out to assess the feasibility of double-injection MRR using the optimized doses, to evaluate the precision of GFR and RPF estimates, and to test the sensitivity of the proposed method in separating kidneys with significant RAS from non-stenotic kidneys. The HIPAA-compliant protocol was approved by the local institutional review board, and written informed consent was obtained from all subjects.

From $N=31$ consecutive patients examined with MRR and MRA between 2004 and 2008 for evaluation of hypertension, we have identified two groups based on the results of renal angiography (Table 1). For each patient, MRA was performed on the same day after dual-injection MRR. The percentage of RAS was measured from source data viewed in multiplanar reconstruction mode on a commercial workstation (Multimodality workplace, Siemens Medical Solutions) by three radiologists independently, and a consensus interpretation was obtained. In Table 1, group A consisted of all patients classified as non-RAS ($N=18$). Group B consisted of all patients with significant RAS (>50% stenosis in at least one renal artery) ($N=8$). Patient characteristics of these two groups were compared using unequal-variance t test. Statistical significance was assumed at $P<0.05$. Patients with mild RAS ($N=5$) were excluded because ACEi-induced renal response in these patients would be difficult to interpret.
All subjects underwent MRR before and after intravenous enalaprilat, according to the protocol described above. Based on the results of simulation (see below), the injected tracer doses for pre- and post-enalaprilat MRR were set as $d_1=4$ ml and $d_2=8$ ml. For three kidneys from three different patients in group A, image segmentation could not be done because of either multiple large cysts or severe motions during scans. For the other 33 kidneys in group A and 10 stenotic kidneys in group B, GFR and RPF for both pre- and post-ACEi studies were successfully measured using the proposed analysis methods described above.

To support the validity of the GFR measurement by MRR, the eGFR by MDRD was computed (14). Single-kidney GFR estimates from pre-ACEi MRR for the two kidneys of each patient were summed to obtain a total GFR (tGFR). Correlation coefficient was used to compare eGFR and tGFR for all the subjects.

Pre-ACEi GFR values for the 33 non-stenotic kidneys in group A were compared with those for the 10 stenotic kidneys in group B, using unequal-variance t test. Similar comparison was done for pre-ACEi RPF. Statistical significance was assumed for $P<0.05$.

For the kidneys in group A (without RAS), the two estimates for each parameter (GFR or RPF) obtained at baseline and after ACEi 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. GFR$_2$-GFR$_1$) across the non-stenotic 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. \((GFR_1 - GFR_2)/GFR_1\), in discriminating non-stenotic and significantly stenotic kidneys.

**Results**

**Simulations**

Figure 2 plots the distribution of \(GFR_2 - GFR_1\) and \(RPF_2 - RPF_1\). As the dose for the first injection (\(d_1\)) increased from 2 ml to 10 ml, the standard deviation (SD) of \(GFR_2 - GFR_1\) (reflecting its precision) first decreased then increased, for both the normal and the dysfunctional kidney scenarios. The minimum SD occurs for \(d_1 = 4\) ml and \(d_2 = 8\) ml. The same behavior of SD is observed for RPF (Figure 2 B). At \(d_1 = 4\) ml and \(d_2 = 8\) ml, \(GFR_2 - GFR_1\) has comparable and minimal bias, less than 1 ml/min for both normal and dysfunctional cases. The biases for \(RPF_2 - RPF_1\) at \(d_1 = 4\) ml are about half of those at \(d_1 = 6\) ml. Overall, the optimal dose distribution appears to be \(d_1 = 4\) ml and \(d_2 = 8\) 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 GFR\(_2\) is less than 8% across all dose distributions (Figure 3 A and B). The conventional subtraction method underestimates GFR\(_2\) by an amount that progressively increases as \(d_1\) increases, reaching an error larger than 60% for \(d_1\) of 10 ml (Figure 3 A and B). At \(d_1\) of 4 ml, the accuracy of GFR\(_2\) 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 RPF$_2$ estimates increases as $d_1$ increases (Figure 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 $d_1 = 4$ ml and $d_2 = 8$ ml, the accuracy of RPF$_2$ 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 Figure 4. Two MRR acquisitions were performed, first using $d_1 = 4$ ml and the second, starting 10 min after the conclusion of the first, using $d_2 = 8$ 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 ml 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 (prior to) the second injection (20 min). With the residues appropriately handled by the initial-value model (Equation (6)), the cortical and medullary concentration versus time curves from the second MRR acquisition were well fitted, with relative RMS error 7.0% for cortex and 8.0% for medulla.

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, \( P=0.011 \), Figure 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 renal artery stenosis (group A), GFR\(_1\) estimates correlated well with GFR\(_2\) estimates (Figure 6 A, 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 ml/min and 7.8 ml/min (Figure 6 B). 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 (Figure 6 A). 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 \((\text{GFR}\(_2\)-\text{GFR}\(_1\))/\text{GFR}\(_1\)\) resulted in 80% sensitivity and 94% specificity for detecting significant RAS.

RPF estimates of the non-stenotic patients in group A show a correlation coefficient 0.870 before and after ACEi (Figure 7 A, 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 ml/min and 76.9 ml/min (Figure 7 B). 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 MR renography offers the opportunity to improve the diagnosis of RVD by providing functional information to complement vascular imaging using MR angiography. 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 renovascular disease.

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 minutes to keep the MRR portion of study within 30 minutes. 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 \((d_1=4\text{ml}, d_2=8\text{ml})\) the second GFR is systematically underestimated by 7.4\%~8.9\% \((8.9\pm8.6\% \text{ for the normal kidney and } 7.4\pm15\% \text{ for the dysfunctional one})\). Given that a threshold of about 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 \(~1\% \text{ (0.7\% for normal and 1.2\% for dysfunctional kidney) }\) systematic error in GFR\(_2\). 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 GFR\(_2\) were comparable \((0.4\pm4.6 \text{ ml/min versus } 0.3\pm3.5 \text{ ml/min})\), supporting the validity of the proposed method.

In our patient study, total GFR \((t\text{GFR})\) derived by MRR (baseline values before ACEi) correlated only moderately with the estimated GFR \((e\text{GFR})\) by the formula of MDRD \((R = 0.522)\). This
may be due to the fact that serum creatinine level doesn’t reliably reflect renal function in elderly patients (23).

Our study of patients without RAS (group A) confirmed good agreement between GFR\(_1\) and GFR\(_2\), with correlation coefficient of 0.931 and GFR\(_2\)-GFR\(_1\) averaging -0.8±4.4 ml/min or 2.7%±14.9% of GFR\(_1\). These results are promising 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 GFR\(_2\)-GFR\(_1\) averaging -8.3±6.9 ml/min (or -26.2%±43.9% of GFR\(_1\)).

Based on current study, the estimated standard deviation of the difference GFR\(_2\)-GFR\(_1\) in the non-stenotic 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 GFR\(_1\) (multiple patients in this study had low GFR\(_1\)). This level of precision compares favorably with plasma clearance methods in nuclear medicine. Using multiple-sample method, Piepsz et al measured a precision of 9.0 ml/min/1.73m\(^2\) for \(^{51}\)Cr-EDTA clearance, and a precision of 53.7 ml/min/1.73m\(^2\) for \(^{99m}\)Tc-MAG3 clearance (18). 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 sec) 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 nephrogenic systemic fibrosis (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 injection combined). Even with Gd-MRA using a single dose, the total dose is less than 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-DO3A). Based on current data, Gd-HP-DO3A 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

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References


Figure Legends

Figure 1. Schematic diagram of 3-compartment model. A: intra-renal arteries; P: proximal tubule; L: loop of Henle. RPF represents the flow rate into A, and GFR the flow rate from A to P. Solid arrow denotes tracer flow, and dashed arrow denotes water reabsorption.

Figure 2. Monte Carlo simulated estimates of renal function expressed as differences in renal function between first and second MRR acquisitions using d₁ for the first injection and assuming a total dose of 12 ml (d₂ = 12 ml – d₁). Plots show the simulated changes in renal function: (A) GFR₂ – GFR₁ and (B) RPF₂ – RPF₁ for each combination of doses and for two scenarios, a normally functioning kidney and a dysfunctional kidney. In this simulation, the true values of GFR₂ – GFR₁ and RPF₂ – RPF₁ are zero. Error bars denote mean value plus and minus one standard deviation.

Figure 3. Monte Carlo simulated estimates of renal function parameters (mean ± SD) for the second of two MRR acquisitions: A-B, GFR₂ of the normal and the dysfunctional kidneys, C-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 Eq. (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, 8] ml, the proposed initial value method reduces measurement bias while preserving the precision of GFR and RPF.

Figure 4. Measured double-injection MRR data and model fits for a representative kidney. A: Tracer concentrations measured from an aortic ROI. 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 Equation (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 zero.

Figure 5. Correlation of eGFR (by MDRD) and tGFR (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.

Figure 6. Comparison of baseline GFR (GFR₁) and second injection GFR (GFR₂) measured using a dual injection MRR protocol. A: correlation plot and linear regression. For the non-stenotic kidneys (displayed as circles), correlation coefficient is 0.931, and regression line y = 1.00x – 0.77 (dashed line); for the stenotic kidneys (triangles), correlation coefficient is 0.870, and regression line y = 0.52x + 1.67 (dotted line). The solid line is the identity line. B: Bland-Altman plot. Difference between the two GFR estimates for the non-stenotic kidneys (displayed as circles) averaged -0.8 ml/min with 95% confidence interval between -9.3 ml/min and 7.8 ml/min (dashed lines). Differences between the two GFR estimates for the stenotic kidneys are shown as triangles.

Figure 7. Comparison of baseline RPF (RPF₁) and second injection RPF (RPF₂) measured using a dual injection MRR protocol. A: correlation plot and linear regression. For the non-stenotic
kidneys (displayed as circles), correlation coefficient is 0.870, and regression line \( y = 0.75x - 0.77 \) (dashed line); for the stenotic kidneys (triangles), correlation coefficient is 0.870, and regression line \( y = 0.75x + 47.5 \) (dotted line). The solid line is the identity line. B: Bland-Altman plot. Difference between the two RPF estimates for the non-stenotic kidneys (displayed as circles) averaged 9.2 ml/min with 95% confidence interval between -58.6 ml/min and 76.9 ml/min (dashed lines). Differences between the two RPF estimates for the stenotic kidneys are shown as triangles.
Table 1. Demographic and functional characteristics of the study population

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<th>Patients without RAS (group A)</th>
<th>Patients with RAS (group B)</th>
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<td>No. of patients</td>
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<td>Sex (M+F)</td>
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<td>Weight (kg)</td>
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<td>Systolic pressure (mmHg)</td>
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<td>Diastolic pressure (mmHg)</td>
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<td>Creatinine level (mg/dL)</td>
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<td>Baseline eGFR (ml/min/1.73m²)</td>
<td>68.9±31.6</td>
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Table 2 Comparison of pre-ACEi GFR and RPF for non-stenotic kidneys and significantly stenotic kidneys in patient study

<table>
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<tr>
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<td>RPF (ml/min)</td>
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<td>GFR (ml/min)</td>
<td>30.7±11.1</td>
<td>20.9±11.9</td>
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