Renal function measurements from MR renography and a simplified multicompartmental model

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Submitted 31 August 2006; accepted in final form 1 January 2007

Recently developed MR imaging (MRI) techniques monitor the transit of gadolinium contrast agents through the kidney. The behavior of gadolinium chelates, such as gadopentetate dimeglumine (Gd-DTPA), is similar to that of inulin; gadolinium chelates are freely filtered at the glomerulus without tubular secretion or resorption. Thus their kinetics can be used to determine physiological parameters such as GFR (10). Some laboratories have used MR to calculate the renal extraction fraction of gadolinium chelates on the basis of flow and concentration measurements in the renal artery and vein or inferior vena cava (9, 11, 13, 28). In a more direct approach, high-temporal-resolution T1-weighted three-dimensional imaging can be used to visualize the passage of gadolinium chelates through intrarenal regions in near real time. The physiological parameters are then determined from quantitative analysis of MR renography signal intensity data. Low doses of contrast material ensure that the signal loss that can be associated with concentrated gadolinium chelates (T2* effects) is avoided and make MR renography compatible with routine clinical contrast-enhanced imaging of the kidneys and renal arteries (24).

MR renography analysis can be performed using methods of varying complexity, such as an analog of Gates’ method adapted from nuclear medicine (22, 23), approaches derived from two-compartment models (1, 5, 18), including the Patlak-Rutland method (17), and multicompartmental modeling methods (8, 20). Multicompartmental kinetic modeling is one of the most sophisticated and versatile tools for the analysis of biomedical systems (4, 37, 38). However, application of kinetic modeling to analysis of in vivo imaging using exogenous contrast agents is challenging. It requires that the model represent the biological system in terms of compartments that are functionally homogeneous, that specific compartments should correspond to regions of interest defined on images, and that the system of compartments be suitably parsimonious to allow for analytic solutions that are physiologically meaningful, numerically stable, and fit experimental data (21). Once these conditions are met, multicompartmental models have potential beyond alternative methods to elucidate broader physiological meaning from imaging data.

We propose a technique for measuring renal function based on a multicompartmental model that recapitulates nephron physiology. We analyze the reliability of parameter determinations from the model and test the results of this approach...
RENAL MODEL

MR renography produces information about tracer concentration vs. time for specific anatomic regions: cortex, medulla, and pelvis. The three-dimensional imaging volume includes both entire kidneys and the abdominal aorta and can be updated as frequently as every 3 s. A measured aortic enhancement vs. time curve serves as the input function for the model. The full multicompartmental model of the vascular-nephron system is briefly introduced, and a simplified and practical model is proposed for measurement of six functional parameters that include renal plasma flow (RPF) and GFR.

Complete Model: Seven Compartments

The full multicompartmental model (Fig. 1) divides the vascular-nephron unit into seven compartments: the intrarenal arteries and glomerular vessels (A), vasa recta and veins (V), proximal convoluted tubule (P), loop of Henle (L), distal convoluted tubule (D), collecting ducts (CD), and calyces and renal pelvis (U). Measurements of signal from the abdominal aorta serve as the aortic input function [Ao(t)]. Concentrations of gadolinium contrast material in each compartment X (mM) are a function of time [X(t)]. Concentrations are related by a system of linear differential equations that express the conservation of mass of the contrast material. The model assumes compartments have fixed volume and instantaneous mixing. For two compartments, concentrations can be directly estimated from imaging: U(t) by concentration measurements from the renal pelvis and V(t) from the renal vein. With extravasal gadolinium chelates used as tracers, the interstitium is assumed to be contained within the vascular (V and A) compartments.

The regional concentration vs. time curves for the cortex and medulla are expressed as linear combinations of compartmental concentrations. The cortical region contains contributions from the A, V, P, D, and CD compartments; the medullary region consists of contributions from the A, V, L, and CD compartments. Each contribution is weighted by the relative volumes of each compartment in the two regions.

The full 7-compartment model contains 17 parameters. Six parameters describe intercompartmental flows: RPF (ml/min), GFR (ml/min), and the flow rates at which the tracer-free filtrate in the various compartments is resorbed into the vasa recta (fP, fL, fD, and fCD). All four tracer-free fluid resorption rates are expressed as fractions of GFR; for example, if 67% of the flow entering the proximal tubule is resorbed within the proximal tubule, 5% within the loop of Henle, 15% within the distal tubule, and 10% within the collecting ducts, then fP = 0.67, fL = 0.05, fD = 0.15, and fCD = 0.10. Nine volume parameters describing six compartments (A, V, P, L, D, and CD) are required to fit measured renal cortical and medullary enhancement data. Three of the compartments are assumed to be fully contained in the renal cortex [P, with volume Vp (ml), and D, with volume VD (ml)] or the medulla [L, with volume VL (ml)]. The A, V, and CD compartments are present in the cortex (Cx) and medulla (Med): VA = VA,Cx + VA,Med, VV = VV,Cx + VV,Med, and VCD = VCD,Cx + VCD,Med.

Two additional parameters necessary for model fitting, the total volume of the cortex (VCx, ml) and the volume of the medulla (VMed, ml), can be measured from the three-dimensional MR images.

Simplified Model for Renal Function Measurements

When the primary goal of the MR renography data analysis is to calculate single-kidney GFR (SKGFR), a simplified version of the model, in which only the A, P, and L compartments are included (Fig. 2), can be used. We describe this abbreviated model and explain the assumptions made to simplify it. All concentrations are expressed per volume of plasma or tubular fluid. Hence, to convert gadolinium concentrations measured in whole blood in the aorta to plasma concentration, we divide by the factor (1 − Hct), where Hct is hematocrit. On the basis of conservation of mass for the indicator and with the assumption that the fluid resorbed from each tubular compartment is free of tracer, the concentrations of gadolinium contrast material in the A, P, and L compartments are expressed as follows:

\[
\frac{dA}{dt} = \frac{RPF}{V_{A,Cx} + V_{A,Med}} \left( \frac{Ao}{1 - Hct} - A \right) \tag{1}
\]

\[
\frac{dP}{dt} = \frac{GFR}{VP} [A - (1 - f_P)P] \tag{2}
\]

\[
\frac{dL}{dt} = \frac{GFR}{VL} [(1 - f_P)P - (1 - f_P - f_D)L] \tag{3}
\]
The A compartment spans the cortex and medulla, and the two the cortex and all loops of Henle are contained in the medulla. As with the full version of the model, this derives six values: GFR, RPF, fP, fL, VA, CX, and VA, Med. Since our preliminary work (see APPENDIX) revealed a high correlation between VP and fP and fL, we chose to constrain two of the parameters: VP/VCx is approximated to be 0.3, and VL/VMed is 0.5 (14, 30). We determined empirically that these ratios resulted in the best fits across all study subjects.

Consequently, for this simplified version of the model, cortical and medullary concentration vs. time curves are fitted to derive six values: GFR, RPF, fP, fL, VA, CX, and VA, Med. Since our preliminary work (see APPENDIX) revealed a high correlation between VP and fP and fL, we chose to constrain two of the parameters: VP/Vcx is approximated to be 0.3, and VL/VMed is 0.5 (14, 30). We determined empirically that these ratios resulted in the best fits across all study subjects.

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phased-array coil on a 1.5-T system with a maximum gradient strength of 45 mT/m (Avanto, Siemens Medical Solutions, Erlangen, Germany). The routine MRI protocol included breath-hold T1- and T2-weighted imaging and contrast-enhanced MR angiography. Before MR angiography, T1 measurements and low-dose gadolinium-enhanced MR renography were performed in all subjects.

**MR renography technique.** MR renography was performed using a coronal interpolated three-dimensional spoiled GRE sequence with the following parameters: TR/TE/flip angle = 2.84 ms/1.05 ms/12°, partition matrix of 161 × 256 interpolated to 256 × 256 with a 425-mm FOV, 20 partitions interpolated to 40, resulting in an interpolated voxel size of 1.6 × 1.6 × 2.5 mm, with parallel factor of 3, bandwidth of 650 Hz/voxel, and 3-s acquisition time. With parallel imaging, 24 reference lines were collected, and images were reconstructed using the generalized autocalibrating partially parallel acquisitions technique (15). To obtain a reliable baseline signal needed for an accurate estimate of tissue concentration, we acquired five three-dimensional images during one 15-s breath hold before contrast injection. To obtain a reliable baseline signal needed for measurement of renal functional parameters, given the presence of measurement errors in MR renography: 1) parameter sensitivity plots, to ensure that the clinically relevant changes in parameter values are reflected in a measurable change in observed data, and 2) Monte Carlo noise simulation analysis, to show that, despite data noise, all parameters can be recovered with clinically useful precision. Sensitivity analyses. We have plotted the relative (percent) change in Cx(t) and Med(t) due to a unit (1%) change in value for each parameter. The sensitivity function with respect to a parameter reflects the relative influence of that parameter on the model fit at each time point across the acquisition period. High sensitivity values are necessary for parameter optimization. The parameters used to generate model curves for the sensitivity analysis were derived from healthy subject 4, with left kidney SKGFR = 68.3 ml/min, and subject 6, with left kidney SKGFR = 17.7 ml/min (as determined by the three-compartment model).

Because differences in cardiac function and hemodynamics can dramatically affect the Ao(t) function, which in turn may also affect model fits, we also determined sensitivity functions for three representative cases of different Ao(t) functions reflecting different degrees of dispersion of the injection bolus (taken from experimental datasets from subjects 1, 3, and 6). The sensitivity functions were calculated using each of the input functions and a fixed set of model parameters selected to reflect a kidney with mild dysfunction: GFR step and 50 ml/min per RPF step. This approach avoids the limitation of many least-squares solvers, which, given noisy data and incorrect starting approximations, may provide an invalid local minimum solution. The residual [root mean square (RMS) error, with equal weights for cortical and medullary data points] was computed for all fits.

**Data Analysis for GFR Measurements**

Regression analysis and Bland-Altman plots were used to compare measurements of SKGFR by MR renography with reference values.

**Parameter Sensitivity and Monte Carlo Analyses of the Model**

We performed two analyses to assess the practical use of our model for measurement of renal functional parameters, given the presence of measurement errors in MR renography: 1) parameter sensitivity plots, to ensure that the clinically relevant changes in parameter values are reflected in a measurable change in observed data, and 2) Monte Carlo noise simulation analysis, to show that, despite data noise, all parameters can be recovered with clinically useful precision.

**Multicompartmental Model for MR Renography**

To determine GFR, RPF, fC, fM, VArm, and VAm, for each kidney, we measured aortic, renal cortical, and renal medullary gadolinium concentration vs. time curves and locally developed software written in C++ to perform a fitting procedure. MR renography data up to 10 min after injection were analyzed. Our program combines the conventional simplex method (27) with a six-dimensional grid of starting parameter values to determine the best least-squares fit of measured data to the model, where, for example, grid steps were 5 ml/min per GFR step and 50 ml/min per RPF step. This approach avoids the limitation of many least-squares solvers, which, given noisy data and incorrect starting approximations, may provide an invalid local minimum solution. The residual [root mean square (RMS) error, with equal weights for cortical and medullary data points] was computed for all fits.

**Analysis of MR Renography Data Using the Three-Compartment Renal Model**

We performed two analyses to assess the practical use of our model for measurement of renal functional parameters, given the presence of measurement errors in MR renography: 1) parameter sensitivity plots, to ensure that the clinically relevant changes in parameter values are reflected in a measurable change in observed data, and 2) Monte Carlo noise simulation analysis, to show that, despite data noise, all parameters can be recovered with clinically useful precision.

**Sensitivity analyses.** We have plotted the relative (percent) change in Cx(t) and Med(t) due to a unit (1%) change in value for each parameter. The sensitivity function with respect to a parameter reflects the relative influence of that parameter on the model fit at each time point across the acquisition period. High sensitivity values are necessary for parameter optimization. The parameters used to generate model curves for the sensitivity analysis were derived from healthy subject 4, with left kidney SKGFR = 68.3 ml/min, and subject 6, with left kidney SKGFR = 17.7 ml/min (as determined by the three-compartment model).

Because differences in cardiac function and hemodynamics can dramatically affect the Ao(t) function, which in turn may also affect model fits, we also determined sensitivity functions for three representative cases of different Ao(t) functions reflecting different degrees of dispersion of the injection bolus (taken from experimental datasets from subjects 1, 3, and 6). The sensitivity functions were calculated using each of the input functions and a fixed set of model parameters selected to reflect a kidney with mild dysfunction: GFR = 40.5 ml/min, corresponding to the right kidney of subject 6.

**Monte Carlo noise simulation analyses.** To evaluate the precision, bias, and pairwise correlation of parameter estimates, the model was used to generate solutions in which we simulated random data noise, varied from 5% to 20% of the mean aortic, cortical, and medullary gadolinium concentrations. The model was then used to fit these pseudodata for which true values of the parameters were known. The variability or standard deviation of each of the fitted parameters in the presence of simulated noise was computed and expressed in terms of coefficient of variation (CV, %). This simulation was performed for the same sets of data used for sensitivity analysis (GFR = 68.3 and 17.7 ml/min).

Monte Carlo noise simulation analyses were repeated for the three Ao(t) functions used in the sensitivity analysis described above.
RESULTS

Three-Compartment Model Fitting of MR Renography Data

Representative images during transit of gadolinium contrast material (which causes signal to increase on the MR images) through the kidney as a result of filtration and excretion are shown in Fig. 4 for healthy subject 4 with normal renal function (serum creatinine = 0.6 mg/dl) and for subject 8 with a history of hypertension and elevated serum creatinine (1.7 mg/dl). Each image is 1 slice from a set of 40 slices, which depicts the entire abdomen, including the abdominal aorta.

Corresponding renal concentration vs. time curves for one kidney of each subject in Fig. 4, together with three-compartment model fits, are shown in Fig. 5. In all cases, cortical and medullary enhancement curves demonstrate an early vascular peak, higher in the cortex than medulla, reflecting the greater arterial perfusion of the cortex. In subject 4 (right kidney GFR = 80.1 ml/min), a second peak in the cortex at 1–2 min reflects accumulation of contrast material in the glomeruli and proximal tubules. This peak is diminished in the case of renal insufficiency in subject 8 (left kidney GFR = 11.3 ml/min). At 2–3 min after injection, medullary enhancement in the healthy kidney is also characterized by a prominent second, broader peak, which reflects the transit of filtered gadolinium contrast agent through the loops of Henle in the medulla. In renal insufficiency, this period of enhancement is delayed, and its amplitude is markedly diminished by comparison.

The three-compartment model fits in Fig. 5 represent the sum of contributions from separate compartments in the model, namely, A and P compartments for the cortex and A and L compartments for the medulla. Each of those components is also plotted for the corresponding data in Fig. 5. The diminished second cortical and medullary peaks are reflected in decreased and delayed enhancement in the P and L compartments, as would be expected in the setting of decreased glomerular filtration.

Fitted values for the six parameters in the model and RMS errors for model fits for the 20 kidneys are given in Table 1. Overall, the three-compartment model resulted in satisfactory fits of measured data. The overall RMS error for fits was 0.007–0.041 mM, where concentrations in the cortex and medulla typically peaked at 0.2–0.3 mM.

Sensitivity Analysis of the Model

Sensitivity functions of the model fits to changes in the fitting parameters are plotted for subject 4 with normal renal function (left kidney GFR = 68.3 ml/min; Fig. 6, left) and subject 6 with diminished kidney function (left kidney GFR = 17.7 ml/min; Fig. 6, right). These plots show the relative change in the model solutions for the cortex and medulla in response to a 1% change in the fitting parameters, except for parameters with values <0.1, where the increment was fixed at an absolute value of 0.01, and demonstrate the relative influence of each parameter at all time points in the acquisition.

The sensitivity to RPF rises sharply to a peak of 0.9% in the cortex and medulla of the healthy kidney at 10 s (Fig. 6, left), which corresponds to the earliest arrival of the contrast material in the tissues (Fig. 5). The sensitivity to RPF then falls rapidly and remains low (<0.1%) from 45 s until the end of the acquisition.

The sensitivity functions for the two parameters that estimate renal blood volumes, $V_{A,\text{Ct}}$ and $V_{A,\text{Med}}$, show maxima of opposite signs early in the acquisition, between 10 and 35 s. At later times (from 90 s), the sensitivity functions to $V_{A,\text{Ct}}$ and $V_{A,\text{Med}}$ remain nearly constant but have different values. The sensitivity of the cortex to $V_{A,\text{Ct}}$ at >90 s remains relatively high (0.3%), while sensitivity of the cortex to $V_{A,\text{Med}}$ is close to zero. In contrast, in the same time interval, the sensitivity of

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Fig. 4. A–D: MR renography in healthy subject 4 (right kidney GFR = 80.1 ml/min, left kidney GFR = 75.0 ml/min). E–H: MR renography in subject 8 (right kidney GFR = 17.2 ml/min, left kidney GFR = 11.3 ml/min). Images depict 1 of 40 slices through both kidneys without enhancement (A and E), at peak cortical enhancement (B and F), at peak medullary enhancement (C and G), and at final excretory phase (D and H).
the medulla to $V_{A,\text{Cx}}$ is nearly zero and the sensitivity to $V_{A,\text{Med}}$ remains nearly stable and does not exceed 0.17%. This difference helps ensure identifiability of both vascular volume parameters in fitting.

Sensitivity functions confirm that the model is quite sensitive to changes in GFR. The wide peak in sensitivity to GFR functions extends between 8 and 150 s in the cortex and reaches the maximum of 0.4% at 35 s. Even greater is the sensitivity to GFR in the medulla, with a maximum spanning 15–225 s and peaking at 1.1% at 50 s, where the medullary concentration reaches its maximum upslope. This time interval is consistent with the period in which the gadolinium chelate bolus travels from the renal cortex to the medulla through the loops of Henle. In the medulla, the sensitivity to GFR exceeds the sensitivity to all other parameters between 40 and 160 s.

Tubular fluid resorption rates ($f_P$ and $f_L$) are associated with the delayed sensitivity maxima at $\sim$300 s, with a greater impact of changes in $f_L$ than $f_P$ on medullary curves and a negligible effect of $f_P$ on cortical curves.

In comparison, for the kidney with lower GFR (Fig. 6, right), the peak in the sensitivity to GFR is broadened (17–250 s) and the maximum sensitivity of the medulla to GFR at 80 s is delayed relative to that of a normal kidney. The amplitude of this peak is also decreased (0.9%). Nevertheless, the sensitivity of the medulla to GFR dominates the sensitivity to other parameters within the important time window of the medullary concentration rise at 1–4 min that enables identification of the GFR value using our model.

Monte Carlo Simulations for Model Fits

To further evaluate parameter identifiability, we performed a Monte Carlo simulation for parameter fitting for the two kidneys described above (Fig. 6): one with normal SKGFR and the other with diminished SKGFR. Table 2 shows the standard deviations of fitted parameter values when $Ao(t)$, $Cx(t)$, and $Med(t)$ were subjected to 5% random noise. The 5% level was selected on the basis of typical signal-to-noise ratios of $\sim$20
The model fits with our MRI technique. At this noise level, estimates of GFR were stable, with a CV of ~5% in the normal and dysfunctional cases. V_A,Cx, V_A,Med, and RPF demonstrated reasonable robustness, with CV of ~10% or less. The tracer-free resorption fractions for the proximal tubules and loops of Henle, f_P and f_L, which are expressed as fractions of GFR, showed higher CV values, given their low unperturbed values. However, the absolute values of the standard deviations of each (<0.06) are low. When the two parameters are combined into a single parameter, 1/(f_P + f_L), reflecting the filtered volume remaining after tubular resorption at the loop of Henle, the combined parameter was remarkably more robust and insensitive to noise, with CV <2.5% (Table 2).

Effect of increased dispersion of aortic input. The model fits were also tested for sensitivity to different degrees of dispersion of the contrast bolus in the aorta. As shown in Fig. 7, separate sensitivity analyses were performed for a fixed set of kidney parameters and three Ao(t) functions (from subjects 1, 3, and 6), which reflect differences in cardiac output that may be independent of renal function (2, 3). The results demonstrate that, with a more dispersed Ao(t) function, the peak medullary sensitivity for GFR is slightly broader and diminished, but the peak remains >0.8%.

Monte Carlo simulation was also performed to assess the effects of different Ao(t) functions on parameter identifiability. We found no difference in the behavior of the fitted parameters for the three Ao(t) functions.

**SKGFR Measurements**

Among the 10 subjects, SKGFR values derived from scintigraphic studies were 3.5–89.4 ml/min. Three-compartment model-derived values were 0–71.0 ml/min. The correlation between model-based SKGFR and reference values was high (r = 0.84, P < 0.001; Fig. 8). Images of one outlier kidney (left kidney of subject 5) revealed several large renal cysts, which may have interfered with the accurate determination of SKGFR by scintigraphy. Without that outlier kidney, the correlation was r = 0.93. Linear regression analysis gave y = 0.76x − 1.14 (y = 0.93x − 6.24 without the 1 outlier case). The Bland-Altman plot revealed that the model-based SKGFR underestimated reference values by an average of 11.9 ml/min, with 95% confidence interval between 5.8 and 9.27 (Fig. 8). Without the outlier, the model values underestimated reference values by an average of 9.4 ml/min, with 95% confidence intervals between 5.5 and 13.3 ml/min.

**DISCUSSION**

Our three-compartment, six-parameter model of the nephron was able to fit a range of patterns of cortical and medullary enhancement in subjects whose SKGFR spanned the wide range typically encountered in clinical practice. RMS errors in fitted curves were typically 0.02–0.03 mM. On the basis of Monte Carlo simulations, image noise contributes modestly to errors in determination of GFR. Other sources of errors include misregistration and blurring artifacts arising from respiratory motion and the simplifications inherent in the model, particularly the combination of arterial and venous (A and V) compartments into the A compartment and the combination of the proximal and distal convoluted tubule (P + D) compartments into the P compartment. As illustrated in Fig. 5 (left), many of the fits underestimated measured data at later time points. We suspect that this occurs because the P compartment is unable to represent accurately the flow of contrast material in the distal tubule and collecting ducts.

### Table 1. Fitted values for the six parameters in the model, including residual RMS fit and reference GFR values

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<th>Subj No.</th>
<th>RMS Error, mM</th>
<th>RPF, ml/min</th>
<th>V_A,Cx, ml</th>
<th>V_A,Med, ml</th>
<th>f_P</th>
<th>f_L</th>
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<td>4.4</td>
<td>4.7</td>
<td>8.0</td>
<td>0.01</td>
<td>0.99</td>
<td>3.5</td>
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RMS, root mean square fit (cortex + medulla); RPF, renal plasma flow; V_A,Cx and V_A,Med, Volumes of compartment A in cortex (Cx) and medulla (Med); f_P and f_L, fraction of tracer-free fluid resorbed at proximal tubule (P) and in the loop of Henle (L); GFR, glomerular filtration rate predicted by the model (Model) and measured by radionuclide renography (Nucl).
We found high correlation between the model-derived MR renographic measurements of SKGFR and reference radionuclide measurement \( r = 0.84 \). The model-derived SKGFR values tended to underestimate reference values by an average of 11.9 ml/min. The degree of underestimation did not correlate with renal function (Fig. 8) or with the goodness of fit (Table 1) and may reflect a limitation of the simplifying assumptions made to generate the six-parameter model. Other possible sources of discrepancies between the two measurements of SKGFR include physiological differences at the times of measurement. We attempted to minimize these by performing both studies on the same morning and by asking the subjects to drink the same amount of water before each study.

For two kidneys (left kidneys of subjects 9 and 10), the MR estimate of SKGFR was zero, while the reference radionuclide measurement was finite (8.7 and 3.5 ml/min). Review of images confirmed visually detectable technetium tracer uptake on radionuclide images and the absence of delayed medullary enhancement after gadolinium administration. Additionally, segmentation of three-dimensional MR images is also confounded by low concentration of the contrast material. Improved accuracy in the estimate of low GFR values may require higher image contrast, for example, by imaging at 3 T or with higher injected doses of gadolinium chelate.

The reference method for SKGFR, radionuclide renography, is also imperfect. With the two-sample approach for global GFR that we used, Rowell and colleagues (31) reported an error of 4 ml/min for global GFR measurements; reliance on scintigraphy to derive split renal function contributes an additional 2–4% CV (26). For our study, more precise determinations of SKGFR using inulin clearance were not considered feasible, given our subject population.

Critical to the application of our multicompartmental model is the conversion of measured MR signal intensity to gadolinium concentration. Our technique is described by Bokacheva et al. (7). It presumes that the concentration of the contrast material does not exceed the level at which signal intensity declines with greater concentration (due to \( T_2^* \) effects), which is expected to hold true given the relatively low doses (4 ml or \(-0.02 \text{ mmol/kg body wt}\)) of gadolinium injected intravenously and short echo times used in the renography sequence. It also assumes fixed relaxivity of the gadolinium and fast exchange of water molecules around the gadolinium. Other approaches have assumed that relative signal intensity changes vary lin-

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**Fig. 6.** Sensitivity functions of cortical (top) and medullary (bottom) gadolinium concentration vs. time curves for the 6 model-fit parameters. Sensitivity functions depict percent changes in model solutions for each region in response to 1% change in a parameter. Sensitivity functions were determined using parameter values derived from fitted values for the left kidney from subject 4 [healthy kidney: model-derived SKGFR = 68.3 ml/min, RPF = 243.3 ml/min, \( f_P = 0.19 \), \( f_L = 0.21 \), volume of A compartment in cortex \( V_{A,Cx} = 20.8 \text{ ml} \), volume of A compartment in medulla \( V_{A,Med} = 6.5 \text{ ml} \)] and the dysfunctional left kidney from subject 6 (diseased kidney: model-derived SKGFR = 17.7 ml/min, RPF = 59.8 ml/min, \( f_P = 0.01 \), \( f_L = 0.15 \), \( V_{A,Cx} = 10.5 \text{ ml} \), \( V_{A,Med} = 4.6 \text{ ml} \)).
early with gadolinium concentration. In regions where gadolinium is concentrated, this assumption may fail.

The simplified three-compartment, six-parameter model that we use is derived from a more complete 17-parameter model that recapitulates the functional units of the vascular-nephron system into seven separate compartments. For derivation of SKGFR, simplification allows for fitting of the cortical and medullary concentration vs. time curves with reasonable accuracy. Sensitivity and Monte Carlo analyses support the ability of the model to identify GFR and RPF with this method.

Identifiability of the tubular fluid resorption parameters \( f_P \) and \( f_L \) is less robust; however, when combined into a single parameter, \( 1/(f_P + f_L) \), they are much less sensitive to noise.

Other models have also been proposed for the analysis of MR renography and have generally focused on estimating GFR. For example, using a Patlak-Rutland approach, Hackstein et al. (17) simulated renal dynamics with two compartments [aorta to kidneys (renal tubules)] to model whole kidney enhancement. Annet et al. (1) used a cortical-compartment model with two compartments (glomeruli to renal tubules) and used only cortical enhancement to estimate GFR. Recently, using these two methods in human subjects, Buckley et al. (8) compared these GFR determinations and found that both highly correlated with reference values; however, both also overestimated GFR considerably. With a model that used separate determinations of cortical and medullary enhancement, Baumann and Rudin (5) modeled the cortex and medulla as distinct compartments, with the rate constant of flow between the two reflecting renal clearance. Other models (18, 36) have also been described. Our model resembles that of Baumann and Rudin, in that the transit of gadolinium from the renal cortex to the medulla is assumed to reflect GFR. However, our model expresses the functional compartments of the nephron explicitly, accounts for compartmental outflow, and has the potential to provide other useful parameters, such as renal perfusion and tubular function.

Several assumptions underlie the proposed six-parameter model. First, the model assumes that the compartments, such as the glomeruli (A), proximal tubules (P), and loops of Henle (L), are well mixed. It ignores, for example, the heterogeneity of the fluid composition along the length of the tubules. The arterioles and glomerular capillaries are combined into one compartment, A, and the heterogeneity of these fluid-filled structures is ignored. Gadolinium contrast rapidly distributes into the interstitial compartment, and, hence, the interstitial compartment is effectively included in the vascular compartment. We observed that the fitted \( V_A \) (arterial and venous volumes) exceeds what would be expected on the basis of histological data, most likely reflecting the interstitial contribution to the volume of distribution. Additionally, as discussed above, the vasa recta are combined into the A compartment in the simplified version (Fig. 3). The volumes of the P and L compartments are approximated using limited histological studies in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Value</th>
<th>SD</th>
<th>CV, %</th>
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</thead>
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<tr>
<td><strong>Functional kidney (GFR = 68.3 ml/min, subj 4 left kidney)</strong></td>
<td></td>
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<tr>
<td>RPF, ml/min</td>
<td>243.3</td>
<td>25.1</td>
<td>10.3</td>
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<tr>
<td>GFR, ml/min</td>
<td>68.3</td>
<td>3.7</td>
<td>5.4</td>
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<tr>
<td>( V_{A,Cx} ), ml</td>
<td>20.8</td>
<td>2.6</td>
<td>12.3</td>
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<td>( V_{A,Med} ), ml</td>
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<td>8.5</td>
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<tr>
<td>( f_P )</td>
<td>0.187</td>
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<td>( f_L )</td>
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<td>337.0</td>
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<td>( 1/(f_P + f_L) )</td>
<td>0.604</td>
<td>0.014</td>
<td>2.3</td>
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</table>

| **Dysfunctional kidney (GFR = 17.7 ml/min, subj 6 left kidney)** | | | |
| RPF, ml/min | 59.8 | 3.0 | 5.1 |
| GFR, ml/min | 17.7 | 0.8 | 4.8 |
| \( V_{A,Cx} \), ml | 10.5 | 0.8 | 8.0 |
| \( V_{A,Med} \), ml | 4.6 | 0.30 | 6.6 |
| \( f_P \) | 0.154 | 0.033 | 21.7 |
| \( f_L \) | 0.010 | 0.034 | 337.0 |
| \( 1/(f_P + f_L) \) | 0.836 | 0.020 | 2.4 |

Effect of 5% random noise added to Ao(t), Cx(t), and Med(t) curves on fitted parameter values for functional and dysfunctional kidney scenarios. CV, coefficient of variation.
humans and animals. We recognize that these are likely to vary across individuals depending on age and disease state (14).

The model assumes that fluids contain tracer or are tracer free. The effects of solutes that pass into and out of the nephron are ignored. The model assumes instantaneous mixing and ignores the tubular length and intratubular concentration variability. Also, the model assumes constant flow between the compartments. This may be reasonable when the modeling is performed over 5–10 min. However, we have observed some notable exceptions. For example, the flow of urine out of the collecting system has a temporal variation over 1–2 min that likely reflects ureteral peristalsis. For the purposes of determining GFR, these variations have a negligible effect on cortical and medullary curves.

With respect to fitting our model to sampled data from MR images, we make some additional important assumptions. From the series of three-dimensional images, the detail afforded by MR renography enables segmentation of the kidney only into renal cortex, medulla, and collecting system (Fig. 4). We are unable to differentiate, for example, the proximal tubule from the distal tubule or the vasa recta from the loops of Henle. The task addressed here can be seen in general terms: to resolve information about the transient movement of a tracer through regions of interest to quantify an organ model consisting of functional compartments. This task is not straightforward when anatomic regions do not map uniquely onto the functional compartments. The essence of the solution is to apportion the transient changes measured experimentally in the region to the functional compartments, which overlap in space. Detail and completeness in the functional model, although desirable, must be balanced against limits on the spatial resolution of the region and variability of the relation between spatial and functional compartments among subjects.

Consequently, for fitting our data, we express the regional concentrations as a composite of compartments. To do so, we make some simplifications. We assume that all glomeruli and proximal tubules are located within the cortex and that all loops of Henle are within the medulla. Image segmentation uses peak cortical enhancement to differentiate the cortex from the medulla; therefore, all regions of the kidney that demonstrate a similar perfusion pattern will be considered cortex. We assume that juxtamedullary glomeruli are included in the cortex. However, we recognize that volume averaging of the voxels that include the cortex and the medulla adds imprecision to our results. Preliminary analysis suggests that these errors result in <10% error in GFR measurements. Further work is needed.

Despite these assumptions, the multicompartmental modeling approach has some distinct advantages. First, the model uses the measured aortic concentration vs. time curve as the input function for the multiple compartments, rather than a gamma variate fit (25). Recirculation of the tracer is inherently included in the fitting. Therefore, the tracer kinetic model can be used to study kidney function independent of cardiac output and vascular dynamics and allows the study to be performed using a minimally invasive intravenous injection of gadolinium contrast. Our analysis shows that measurements of GFR are not sensitive to dispersion of the bolus in the aorta. To derive an accurate aortic curve, our approach assumes the absence of flow-related effects on the MR signal. This is achieved by positioning of our oblique coronal imaging slab in the plane of aortic flow.

Second, because we use a large number of data points from a ≥10-min sampling interval, fits with the model are robust and less susceptible to the effects of noise or motion artifacts in the images. The technique, however, does rely on accurate registration and segmentation algorithms, which can be time consuming if not automated. Several laboratories continue to investigate the development of improved automated image-processing algorithms (12, 32, 34).

Finally, and most importantly, the multicompartmental model has the advantage of broad applicability. Our approach has the potential to provide additional physiological information beyond GFR. Hsu (19) and others have argued that investigators studying renal function should think beyond GFR and explore other parameters that may better elucidate renal pathophysiology. Our approach has the potential for use in the study of RPF and renal blood volume, as well as tubular concentrating ability, expressed in terms of $f_p$ and $f_L$, for example. For some parameters in our model, dedicated valida-

![Figure 8](http://ajprenal.physiology.org/DownloadedFrom/10.220.33.3/June232017)
tion studies are needed. For example, although model-derived estimates of RPF were obtained in this study, we were unable to verify these without separate injections of hippuran or other intravascular radiotracers. The challenge of validating less traditional measures, such as tubular function, remains.

APPENDIX

To demonstrate that the model given by Eqs. 1–5 cannot uniquely determine $V_P$ and $f_P$, we assume a fixed relation between the two values in our implementation of the model. These two parameters control the tracer concentration in the $P$ compartment, which the model assumes to lie entirely in the cortex. The proof is based on the fact that $V_P$ and $f_P$ exhibit similar cortical sensitivity

$$\frac{dC_x}{dV_p} = k \frac{dC_x}{df_p}$$

where $k_1$ is independent of time.

Since it is apparent that tracer concentration in the A compartment ($A$) is not a function of $V_P$ or $f_P$ (see Eq. 1), Eq. 4 implies

$$\frac{dC_x}{dV_p} = \frac{1}{V_C} \frac{d(V_p \cdot P)}{dV_p}$$

and

$$\frac{dC_x}{df_p} = \frac{V_p}{V_C} \frac{dp}{df_p}$$

Given the initial condition of tracer concentration in the proximal and distal tubules (compartment $P$) = 0 at $t$ = 0, we can solve the linear differential Eq. 2 for $P$ in terms of $A$

$$P(t) = \frac{GFR}{V_p} e^{-GFR/(1-f_p)V_p} \int_0^t A(u) e^{GFR/(1-f_p)V_p} du$$

Substituting Eq. A4 in Eqs. A2 and A3 and applying the product rule for the derivatives yields

$$\frac{dC_x}{dV_p} = \frac{GFR^2(1-f_p)}{V_C} e^{-GFR/(1-f_p)V_p} \left\{ \int_0^t A(u) e^{GFR/(1-f_p)V_p} du \right\}$$

and

$$\frac{dC_x}{df_p} = \frac{GFR^2}{V_C} e^{-GFR/(1-f_p)V_p} \left\{ \int_0^t A(u) e^{GFR/(1-f_p)V_p} du \right\}$$

Forming the ratio of Eqs. A5 and A6 establishes Eq. A1, with the constant $k_1 = (f_p - 1)V_p$.

Similar steps can be used to derive the inability of the model to uniquely determine $V_L$ and $f_L$.

As an independent confirmation of the linkage of pairs ($V_P$ and $f_P$) and ($V_L$ and $f_L$), we performed a series of Monte Carlo trials with addition of random noise to tracer concentration in cortex and medulla (Cx and Med, respectively) and observed a perfect correlation (Pearson $R = -1.0$) between $V_P$ and $f_P$ (and between $V_L$ and $f_L$) when both parameters are estimated in fitting Eqs. 4 and 5.

REFERENCES


