Assessment of Renal Function with Dynamic Contrast-Enhanced MR Imaging

Louisa Bokacheva, PhD,*, Henry Rusinek, PhD, Jeff L. Zhang, PhD, Vivian S. Lee, MD, PhD, MBA

The primary functions of the kidneys are to filter and excrete metabolic waste products and maintain homeostasis by regulating acid-base balance, blood pressure, and fluid volume. Assessment of renal function is often required in radiologic diagnosis, mainly for assessment of renal insufficiency, renovascular disease, renal transplants, and abdominal trauma. Noninvasive tests of renal function also can be helpful in longitudinal and translational studies.

Several noninvasive tests of renal function have been developed. These include measurements of serum creatinine level and endogenous creatinine clearance, renal scintigraphy and contrast-enhanced CT. These methods, however, have serious drawbacks. Creatinine indicators are imprecise and depend on body mass and age and cannot assess a single-kidney function. Renal scintigraphy requires radioactive tracers and provides little information about the kidney anatomy. CT has excellent spatial resolution, but exposes the patient to radiation and potentially nephrotoxic contrast agents.

MR imaging provides highly detailed anatomic information and has shown a great promise in noninvasive assessment of the renal function. Dynamic contrast-enhanced MR imaging of the kidney, or MR renography, monitors the transit of contrast materials, typically gadolinium chelates, through the intrarenal regions, the renal cortex, the medulla, and the collecting system (Fig. 1). Most gadolinium contrast agents are cleared by glomerular filtration and pass from the renal vasculature into the renal tubules while enhancing the signal of the renal tissues. Typically, the kidney enhancement shows the following stages: (1) bolus arrival in the large vessels; (2) cortical enhancement (20–30 seconds after administration of contrast) that mostly reflects the contrast within renal vasculature (Fig. 1B); (3) medullary enhancement that usually occurs about a minute later and is dominated by the contrast in renal tubules (Fig. 1C); and (4) enhancement of the collecting system several minutes afterward (Fig. 1D). By analyzing the enhancement of the renal tissues as a function of time (Fig. 2), one can determine such clinically important single-kidney parameters as the renal blood flow (RBF), glomerular filtration rate (GFR), and cortical and medullary blood volumes.

The most widely used gadolinium contrast agent is gadopentetate dimeglumine (Gd-DTPA). It is freely filtered by the glomerulus and is neither reabsorbed nor secreted by the renal tubules, which makes it a suitable marker of glomerular filtration. Until recently, gadolinium contrast agents have been considered safe for all patients. In the past...
few years, however, these contrast agents have been linked with the risk of developing nephrogenic systemic fibrosis, a debilitating and potentially fatal condition that affects patients with renal insufficiency (with total GFR < 30 mL/min/1.73m²). So far, about 250 cases of nephrogenic systemic fibrosis have been reported worldwide. MR renography should be performed with caution in patients with decreased renal function, and whenever possible such patients should be studied with alternative, contrast-free methods.

The MR renography studies performed to date have accumulated a wealth of physiologic and methodologic information relevant for dynamic studies of the kidneys and other abdominal organs. Several excellent reviews of functional renal imaging using MR imaging have been published by Huang and colleagues, Michoux and colleagues, Prasad, and Michaely and colleagues. This article provides an update of the recent developments in T1-weighted, gadolinium-enhanced MR renography and quantification of renal perfusion and filtration based on MR renography data.

**MR RENOGRAPHY: KEY STEPS**

Numerous MR renography studies have been reported in the past few years. Although there is no consensus regarding the optimal procedure, MR renography examination usually consists of the following steps: (1) acquisition of dynamic image series, (2) image postprocessing for motion correction and tissue segmentation, (3) quantification of contrast concentration, and (4) analysis of the concentration versus time data leading to

---

**Fig. 1.** Representative MR renography images of the right kidney of a 65-year-old woman with normal kidney function showing progressive enhancement of kidney tissue (injected dose 4 mL of Gd-DTPA at 2 mL/s; three-dimensional FLASH, TR/TE/FA = 2.84/1.05/12 degrees, voxel volume 1.7 × 1.7 × 2.5 mm³). (A) Unenhanced. (B) Maximum cortical enhancement. (C) Maximum medullary enhancement. (D) Collecting system enhancement.

**Fig. 2.** Signal intensity measured in abdominal aorta (A) and kidney parenchyma, cortex, and medulla (B) for the same patient as in Fig. 1. Rapid first-pass signal changes in aorta and kidneys are sampled every 3 seconds during the first 30 seconds. The whole kidney, cortical, and medullary signal intensity curves show sharper peaks caused by renal vasculature followed by broader peaks caused by the contrast in the renal tubules.
derivation of renal functional parameters. These steps are discussed next.

**Acquisition**

Current MR renography studies typically use T1-weighted, gradient recalled echo sequences. Three-dimensional acquisitions provide continuous whole-kidney coverage and enable assessment of the whole-kidney function, but require longer acquisition times. Two-dimensional images can be acquired with higher temporal and spatial resolution but sample only selected slices. Also, two-dimensional acquisition of a limited number of slices precludes the use of spatial alignment (see later) because there is some anteroposterior renal motion (ie, perpendicular to the customary coronal acquisition plane).

Although most of the published work has been done at 1 to 1.5 T, higher field (3 T) offers better signal-to-noise ratio. The flip angle is usually selected to maximize signal-to-noise ratio and the contrast between the enhanced and unenhanced kidney tissues. This approach favors lower flip angles. For example, for gradient recalled echo sequence with repetition time TR = 3 milliseconds, the cortical signal with unenhanced T1 = 1000 milliseconds is estimated to be about three times higher at flip angle of 12 degrees than at 40 degrees. For an expected maximum cortical contrast concentration of 0.4 mM, the contrast between the enhanced and unenhanced cortical signals is 2.3 times higher for 12 degrees than for 40 degrees. The downside of using lower flip angles is the strong nonlinearity of signal with gadolinium concentration. As an alternative, the flip angle may be chosen to maximize the range and accuracy of the linear relationship between signal and concentration.

One of the greatest challenges in quantitative functional imaging is the measurement of the signal in arterial blood, which plays the role of arterial input required by most tracer kinetic models. The arterial signal is usually sampled in the abdominal aorta and may be affected by the flow-related artifacts. To minimize these effects, imaging can be done in the coronal plane, or magnetic preparation (saturation or inversion) can be added to axial acquisitions.

After collecting several unenhanced images for a reliable estimate of baseline signal, dynamic images are acquired every few seconds during free breathing, during separate breath-holds, or as a combination of both. Rapid changes of blood and tissue signal intensities during the first-pass enhancement are best captured during breath-holding, whereas slower-changing subsequent stages may be acquired with quiet breathing or respiratory triggering. Parallel imaging may be used to improve temporal resolution of MR renography, especially for imaging of the rapid signal changes during the first-pass perfusion, but may provide decreased image quality and is most suitable for imaging when high signal-to-noise ratio is expected. The temporal resolution used in published MR renography studies varies from 1 second during the first-pass phase to 60 seconds during later (excretion) stages. In experiments on healthy volunteers performed with 1-second resolution, Michaely and colleagues have shown that the temporal resolution of at least 4 seconds is required to achieve 10% precision in estimates of renal perfusion and filtration rates. Parameters describing the plasma and tubular volumes proved to be more tolerant to temporal resolution and require 9 second sampling interval to reach 10% precision. Note, however, that estimating the precision of renal functional parameters is a complex task, because the precision depends on many factors, including contrast dose and injection rate, arterial sampling scheme, and the choice of the model for parameter identification.

The total acquisition time of MR renography series is 3 to 10 minutes with longer time needed to characterize more distal portions of the nephrons. Shorter acquisition time (20–30 seconds) is sufficient for estimates of renal perfusion, intermediate acquisition time of 2 to 5 minutes for assessment of the filtration and tubular properties, and the longest acquisition time is required for characterization of the collecting system. In healthy volunteers, Michaely and colleagues estimated that acquisition time of at least 35 seconds is required to characterize plasma flow, acquisition time of 85 seconds is needed for plasma volume, 230 seconds for tubular flow, and 255 seconds is needed for tubular volume characterization with precision of 10% or better. Longer acquisition times are needed in patients with decreased renal plasma flow (RPF) and GFR.

T1-mapping is sometimes performed before MR renography to determine the unenhanced T1 values of the renal tissue for quantification of contrast concentration (Fig. 3). Because three-dimensional T1-mapping within one breath-hold is technically challenging, this measurement is frequently done on a single representative slice through the kidney. Available T1 measurement methods include dual flip gradient echo angle technique, conventional inversion recovery methods, inversion-recovery prepared low-flip angle TrueFISP, the Look-Locker method, and T1 fast acquisition relaxation mapping.
Contrast Dose

Many groups use standard doses of gadolinium for MR renography (0.1–0.2 mmol/kg). There is considerable evidence, however, that lower contrast doses do not compromise the precision of renal functional parameters. Using Monte Carlo simulations, the authors’ group determined the relationship between the contrast dose and the precision of renography-derived GFR. According to this analysis, injected doses of Gd-DTPA above approximately 1.5 to 2 mmol do not result in increased precision of GFR (Fig. 4). The highest GFR precision is achieved at approximately 0.02 mmol/kg dose in normal patients, and approximately 0.025 mmol/kg in patients with decreased renal function. Several studies demonstrated the feasibility of MR renography with ultralow doses (ie, doses that are up to 10 times lower than the standard ones), and showed that these doses help to avoid the susceptibility effects associated with concentrated gadolinium in renal medulla and collecting system.

Quantification of Contrast Concentration

Kinetic modeling requires that the MR renography signal be converted into gadolinium concentration. This conversion presents a challenge because in addition to contrast concentration, MR signal intensity varies with the pulse sequence parameters; the precontrast relaxation times; and in the case of blood, the flow velocity. Moreover, the relationship between signal and concentration is in general nonlinear. At higher contrast concentrations, the susceptibility may cause the signal intensity to decrease with increasing concentration.

The simplest approach is to express gadolinium concentration as the relative enhancement

$$[\text{Gd}] = k \frac{S(t) - S(0)}{S(0)}$$

where $S(0)$ and $S(t)$ are the baseline (at time $t = 0$) and the contrast-enhanced ($t > 0$) signal intensities, respectively. The tissue-dependent constant $k$ can be derived from phantom measurements. As the concentration increases, however, this linear relationship is associated with progressively increasing errors.

Gadolinium concentration can also be computed from analytic expressions of signal intensity. For example, the spoiled gradient echo signal intensity is given by

$$S(t) = S_0 \sin^\alpha \frac{1 - e^{-R_1(t)TR}}{1 - \cos^\alpha \cdot e^{-R_1(t)TR}}$$

where $S_0$ is the equilibrium signal, $\alpha$ is the flip angle, TR is the repetition time, and $R_1 = 1/T_1$ is the longitudinal relaxation rate. Equation 2 can be solved for $R_1(t)$, enabling $[\text{Gd}]$ to be derived from the relationship:

$$R_1(t) = R_1(0) + [\text{Gd}] r_1$$
where $R_1(0)$ is the longitudinal relaxation rate of tissue before contrast injection and $r_1$ is the specific relaxivity of the contrast agent. The specific relaxivity of a contrast agent required by equation 3 may depend on the surrounding medium, and in vivo measurements of relaxivities are particularly challenging. Specific relaxivities of commonly used contrast agents were recently measured at different fields, temperatures, and in different media (water, saline, plasma, whole blood). The resulting relaxivities were somewhat lower than the previously used values. Rohrer and colleagues found for Gd-DTPA at 1.5 T and $37\text{°C}$, $r_1 = 4.1 \, (\text{mmol/L})^{-1} \, \text{s}^{-1}$ in plasma and $4.3 \, (\text{mmol/L})^{-1} \, \text{s}^{-1}$ in whole blood. At 3 T and $37\text{°C}$, the plasma $r_1$ was decreased to $3.7 \, (\text{mmol/L})^{-1} \, \text{s}^{-1}$. Pintaske and colleagues obtained similar values, also for Gd-DTPA at $37\text{°C}$ in plasma: at 1.5 T $r_1$ was $3.9 \, (\text{mmol/L})^{-1} \, \text{s}^{-1}$, and at 3 T $r_1$ decreased to $3.3 \, (\text{mmol/L})^{-1} \, \text{s}^{-1}$.

Alternatively, the relationship between the signal intensity and $T_1$, denoted $f(T_1)$, may be determined empirically by imaging a gadolinium-doped water phantom, either imaged separately or together with the subject. The tissue signal intensity is assumed to be proportional to $f(T_1)$ scaled by a numerical factor $g$, which depends on system gain, coil sensitivity, and patient habitus:

$$S = g \cdot f(T_1) \quad (4)$$

The coefficient $g$ can be found from a pair of closely matched signal and $T_1$ measurements (eg, acquired before the injection of contrast). The authors have shown that for a three-dimensional fast low angle shot (FLASH) sequence the phantom-derived $f(T_1)$ dependence is similar to this relationship in human tissues (Fig. 5). Compared with the concentrations determined by direct $T_1$-mapping, concentrations calculated from in vivo MR renography signal intensity measurements agreed on average within 13% ($r = 0.99$) up to 1.4 mM when the phantom-based conversion method was used, whereas the relative enhancement conversion progressively underestimated the concentrations above 0.8 mM by 20% or more.

Signal calibrations with static phantoms do not account for all variations of the signal intensity,
because of rapid flow in large blood vessels. The inflow of fresh blood with fully polarized spins causes the flow-related signal enhancement, which may result in incorrect arterial concentration and errors in renal functional parameters. To account for inflow effects, Ivancevic and colleagues performed signal intensity versus concentration measurements at varying flow velocity in flow phantoms and applied this calibration to renal perfusion imaging. The calibration had a particularly strong effect on the concentration at the bolus peak. In the phantom, the bolus peak concentration obtained with static calibration was 3.2 times higher than the flow-corrected value, which was not significantly different from the directly measured concentration. In axial fast gradient echo acquisitions performed in patients, without the flow correction, the peak aortic concentration measured at systole was 2.5 times larger than at diastole. When flow-corrected conversion was used, the difference between systolic and diastolic measurements became insignificant. The discrepancy between systolic and diastolic measurements of the bolus peak concentration was reduced from 180% ± 37% with static calibration to 21% ± 15% with flow correction.

Coronal acquisitions may help minimize the inflow effect. As an alternative, some groups have investigated the use of population-based arterial curves. Parker and colleagues derived an average aortic curve from 67 MR imaging examinations of 23 cancer patients and obtained 40% narrower confidence intervals in repeated intraindividual measurements of perfusion parameters than with the individually measured arterial input. Wang and colleagues reported an excellent correlation (r >0.99) and no significant differences between perfusion parameters derived with individually measured and averaged arterial input functions sampled in femoral arteries of patients with osteosarcomas. This approach may be more successful with relatively uniform populations.

**Image Analysis**

MR renography image postprocessing typically consists of image coregistration and segmentation. Coregistration involves spatial aligning of the renal images at different time points, and segmentation is often required to identify the anatomic subregions of the kidney. The demands for image segmentation depend on the method of analysis. Some groups use renal cortex and others also use renal medulla signal to derive measures of renal function from MR renography. Whole kidney data are the simplest to obtain.

Absence of reliable image analysis software is one of the factors that limit implementation of MR renography in clinical practice. Segmentation may simply involve manual drawing of regions of interest. Manual segmentation, however, is tedious, time-consuming, and requires anatomic expertise. Moreover, if only small subregions are sampled, the total renal volume required for GFR and RPF estimates remains unknown and the resulting enhancement curves may not be representative of the entire organ. Alternatively, using automated or semiautomated algorithms, the entire kidney may be segmented from the surrounding tissues and collecting system, and the renal parenchyma may be further divided into cortex and medulla (Fig. 6).

A semiautomated tissue segmentation algorithm developed by Boykov and colleagues enables segmentation of MR renography images into cortex, medulla, and collecting system regions based on an interactive graph cuts approach. Rusinek and colleagues assessed the accuracy and precision of segmentation with this algorithm applied to simulated and in vivo data in comparison with manual segmentation performed by experienced readers. The semiautomatic segmentation produced a slight systematic oversegmentation of cortex at the expense of cortex and medulla.

**Fig. 6.** Three-dimensional renderings and orthogonal views of renal tissue segmented using level sets algorithm of Song and colleagues. (A) Whole kidney. (B) Medulla. (C) Renal pelvis.
of medulla (volume errors of about 10% in the cortex and 21% in the medulla relative to their true volumes). The precision of the segmentation was on average 5% in the cortex and 7% in the medulla. RPF and GFR derived from these data using a tracer kinetic model were determined with clinically acceptable accuracy and precision (both below 10% for RPF and below 15% for GFR). The processing time was reduced from 2 to 3 hours required for manual processing to about 21 minutes per kidney using semiautomatic segmentation.

As an alternative to tissue segmentation, a voxel-by-voxel analysis has also been applied to MR renography. With this approach, the signal intensity in each voxel is traced across all time points and analyzed with an appropriate method. This approach provides local information about the kidney function and usually eliminates the need for a separate segmentation step, but is more computationally intense and more susceptible to misregistration errors and signal noise than segmentation-based analysis. Also, voxel-based analysis does not evaluate the whole-kidney function, unless followed by further processing steps.

RENAL PERFUSION QUANTIFICATION: CLINICAL APPLICATIONS

Assessment of renal perfusion is helpful in several renal diseases: for assessment of renal artery stenosis (RAS) and in renal transplant dysfunction (chronic ischemic nephropathy, drug nephropathy). Several methods have been used to quantify the renal perfusion from MR renography, such as the upslope method, semiquantitative parametric methods, deconvolution methods, and various compartmental models. It has to be noted, however, that low-molecular-weight contrast agents, such as Gd-DTPA (molecular weight 590 d), quickly leak from the bloodstream into the extracellular extravascular space and may provide incorrect estimates of perfusion. More accurate perfusion measurements may be obtained using intravascular contrast agents described in the next section.

The upslope method has been initially devised by Peters and colleagues for nuclear medicine and adapted for MR imaging. It is based on a simplified picture of contrast behavior akin to microspheres: the tracer flowing into the kidney is assumed to remain in the kidney vasculature. This “inflow only” approximation is valid until the contrast begins to flow from the renal vasculature into the renal tubules. RBF can be found as the maximum slope of the kidney curve divided by the peak arterial concentration:

\[
RBF = \frac{\text{maxslope}(K(t))}{\text{max}(A(t))} \quad (5)
\]

Montet and colleagues used the upslope method to estimate the cortical RBF from dynamic MR imaging in nine rabbits. Reference RBF values were measured in the renal artery using an ultrasound flow probe. Experiments were performed at baseline and after a modification of the RBF by an intervention, either by mechanical RAS (ipsilateral to the flow probe) or administration of hyperosmolar agents (injections of dopamine or angiotensin II, or colloid infusion). The results demonstrated the benefits of taking into account the arterial input as opposed to using the maximum upslope of the kidney concentration curve alone as a measure of renal perfusion. The ultrasound RBF measurements correlated considerably better with the absolute RBF estimates \((r = 0.80)\) than the maximum upslope of the kidney curve \((r = 0.53)\).

Valeé and colleagues applied the upslope method to quantifying RBF in 27 subjects with normal kidneys, well-functioning renal transplants, and kidneys with RAS and renal failure. For functioning kidneys, the average blood flow was found to be \(2.54 \pm 1.16 \text{ mL/min/g}\) in the cortex and \(1.08 \pm 0.50 \text{ mL/min/g}\) in the medulla. In transplanted kidneys both cortical and medullary flows were increased by 30% to 40% compared with native kidneys. Compared with all functioning kidneys (native and transplant), cortical and medullary flows were 50% to 60% lower in kidneys with RAS and 70% to 80% lower in patients with renal failure.

Pedersen and colleagues compared the upslope estimates of RBF in rats subjected to either unilateral renal artery occlusion or partial ureteral obstruction against rats in which the left ureter was dissected 1 hour before MR imaging (sham-operated). Normalized to the intact side, RBF on operated side was the lowest in kidneys with arterial occlusion \((0.35 \pm 0.02)\); slightly higher in kidneys with obstructed ureters \((0.40 \pm 0.03)\); and the highest in sham-operated kidneys \((0.49 \pm 0.01)\).

The advantage of the upslope method is its simplicity, whereas its main drawback is the need to measure the maximum of the arterial concentration, which is unreliable. The limited amount of data used for analysis, usually the first 20 to 30 seconds after injection, makes it more susceptible to errors, especially at low temporal resolution. The inflow-only approximation may be invalid in well-perfused kidneys beyond the first few seconds after the bolus arrival.
Feasibility of semiquantitative, parametric evaluation of patients with renal artery stenosis (RAS) was reported by Michaely and colleagues. The two-dimensional data were acquired with saturation-recovery TurboFLASH sequence at 1-second temporal resolution for at least 4 minutes. High-resolution MR angiography served as the reference technique for detection and grading of RAS. Kidney enhancement curves were fitted with an empiric expression that consisted of a gamma variate function to describe the first-pass perfusion and a double-exponential function to describe the filtration. Four curve parameters were derived from voxel-by-voxel fitting: (1) time to peak, (2) mean transit time (MTT), (3) maximum upslope, and (4) maximum signal intensity. Significant differences were observed in maximum upslope, MTT, and time to peak between the combined group of normal and low-grade RAS versus the high-grade RAS, but kidneys without RAS and those with low-grade RAS could not be distinguished. MTT and time to peak correlated strongly \( r = 0.96 \), and time to peak and maximum upslope showed moderate negative correlation \( r = -0.6 \). Highly significant, but moderate correlations were found between all four parameters and serum creatinine \( r \) approximately 0.4–0.5. Maximum upslope voxel maps enabled detection of segmental perfusion deficits in three kidneys in areas confirmed to be ischemic by biopsy.

Deconvolution approach to calculation of renal perfusion and filtration was used by Hermoye and colleagues. MR renography experiments were performed in six rabbits with a saturation-prepared turbo field echo sequence at 1.1-second temporal resolution. After phantom-based conversion, the arterial input was numerically deconvolved from the cortical curve. The resulting cortical impulse response function was expected to exhibit three peaks corresponding to the contrast passing sequentially through the glomeruli, proximal convoluted tubules, and distal tubules. The vascular and the proximal tubules peaks were fitted by a sum of two gamma variate functions. The fractional plasma volume and the vascular MTT were determined from the area under the curve and the washout rate of the vascular curve. The renal perfusion was found as the ratio of fractional plasma volume to MTT and correlated well with the results of the upslope method \( r = 0.9 \). As expected for numerical deconvolution, the errors in RPF and other parameters were shown to increase dramatically with noise level. At 5% noise, the error in RPF was about 20% relative to the ideal value, and at 10% it increased to about 50%.

The feasibility of voxel-based deconvolution analysis of MR renography in human kidneys was demonstrated by Dujardin and colleagues. The perfusion parameters were determined in 14 volunteers and 1 transplant patient using inversion-recovery prepared TurboFLASH sequence. A flip angle of 50 degrees was used to improve the linearity of the signal versus concentration. The arterial input function was numerically deconvolved from the renal curves to determine the impulse response function in every voxel. The maximum of the impulse response function, the area under the impulse response function curve, and the ratio of the integral to the maximum were respectively interpreted as RBF, renal volume of distribution, and MTT. The average shape of observed impulse response function was similar to that obtained by Hermoye and colleagues. In native kidneys RBF was 1.6 mL/min/mL and ranged from 0.8 and 4.5 mL/min/mL. Cortical RBF was found to be three times higher than the medullary RBF. Both the perfusion and the cortex-to-medulla ratio were lower than those reported elsewhere. This underestimation was attributed to deconvolution errors, dispersion of the aortic bolus, and the inflow artifact in the aorta.

A two-compartment model proposed by Annet and colleagues, in which the concentration in renal vascular compartment is determined by dispersion and delay of the aortic bolus, enables calculation of vascular volume and RBF (Fig. 7). The experiments of Annet and colleagues, however, focused on assessing renal filtration, and perfusion estimates were not reported.

The reviewed results suggest that both semiquantitative and fully quantitative measures of perfusion can be useful in assessment of renal function. Semiquantitative parameters, such as the time to peak and maximum upslope, are usually robust and easy to assess, but have limited physiologic interpretation and cannot always be compared across different patients. The quantitative perfusion methods include simple inflow models, compartmental models, and deconvolution methods. The upslope method is simple, but relies on the initial part of the first-pass peak, which often contains just few data points, and on the inflow-only approximation, which may not be valid in the kidney beyond the first few seconds after the bolus arrival. The numerical deconvolution methods are sensitive to noise, more so than the compartmental models. All of the quantitative methods require measurements of the arterial input function, which may be unreliable because of sampling errors and inflow artifacts. Because the arterial input function is usually sampled in the aorta, the dispersion and delay of the bolus.
confounds the modeling. As a result, renal perfusion estimates are highly sensitive to the variations of the arterial input. Comparisons of the MR renography–derived perfusion against other established methods are needed.

**Renal Perfusion Imaging using Intravascular Contrast Agents**

Unlike the low-molecular-weight contrast agents, such as Gd-DTPA, which quickly distribute over the interstitial space, the so-called “intravascular contrast agents” stay in the bloodstream for a considerably longer time. Because these agents have not yet been approved for clinical use, data mostly from animal experiments are available, although few human studies also have been reported.

Prasad and colleagues\(^57\) reported perfusion measurements using MS-325 (EPIX Medical, Cambridge, Massachusetts), a gadolinium-based intravenous contrast agent that binds to serum albumin in plasma. Protein binding reduces leakage of contrast out of the vasculature and increases the half-life of contrast in plasma. Pigs with surgically induced RAS were injected with MS-325 and imaged with turbo-FLASH sequence, and cortical blood flow and MTT were estimated from the first-pass perfusion data using the upslope method. The resulting perfusion measurements agreed well with the reference microsphere experiments (258 mL/100 g/min versus 198 mL/100 g/min, respectively), but neither indicated any significant reduction in cortical perfusion over 5 weeks after surgery, which may be attributed to the ability of the kidney to regulate blood flow.

Aumann and colleagues\(^55\) used the intravenous ultrasmall particle iron oxide contrast agent NC100150 to measure perfusion in eight dogs with ultrasound flow probes implanted at the origin of the left renal artery. This agent is cleared from blood by reticuloendothelial system and is not at all filtered by the kidney. As a result, the kidney enhancement reflects only perfusion and is free from the effects of filtration and excretion. Dynamic imaging was performed with a T2*-weighted FLASH sequence (TR/TE/FA=15/6/12 degrees, temporal resolution 1.92 seconds), and ultrasound flow measurement was done immediately before and after the MR imaging measurement. Voxel-based renal perfusion yielded RBF of 524 ± 47 mL/min/100 g versus the ultrasound-measured value of 403 ± 72 mL/min/100 g with moderate correlation (\(r = 0.71\)). The renal blood volume was found to be 27 ± 3.6 mL/100 g and the MTT was 3.4 ± 0.5 seconds. The MR imaging perfusion measurements overestimated both the blood flow and the blood volume compared with generally accepted values.

In a subsequent study, Schoenberg and colleagues\(^56\) applied a similar measurement technique and the same contrast agent to dogs with surgically induced RAS and in humans with long-standing RAS. The baseline RBF in dogs was 496 mL/min/100 g and remained almost unchanged for stenosis up to 50% and decreased to 379 mL/min/100 g at stenosis of 80%. At further reduction of renal artery diameter to above 90%, RBF dropped to 151 mL/min/100 g. In human kidneys with parenchymal damage caused by RAS, RBF was considerably lower than in normal kidneys (166 mL/min/100 g versus 379 mL/min/100 g, respectively), whereas the blood volume was slightly lower in kidneys with RAS than in normal ones.

**GLOMERULAR FILTRATION RATE**

A variety of methods have been proposed for quantification of renal filtration, ranging from simpler upslope models, to more complex compartmental models (Fig. 8). These models share some common assumptions. The kidney is usually represented as a combination of at least two
homogeneous compartments, vascular and tubular, and GFR is found as the flow of contrast from the vascular into the tubular compartment.

Baumann and Rudin\(^\text{58}\) proposed an inflow-only model in which the contrast flows from cortex to medulla with the rate given by the filtration coefficient (Fig. 8A). The cortex plays the role of the vascular compartment, and the medulla that of the tubular compartment. The outflow of contrast from the medulla is ignored. In experiments on rats, Laurent and colleagues\(^\text{59}\) have shown that the filtration coefficient correlated with GFR measured by inulin clearance \((r = 0.75)\). A related model has been recently proposed by Zhang and colleagues.\(^\text{60}\) Aorta, cortex, and medulla are concentrations in blood and renal tissues; plasma, tubules, proximal tubules, and loops of Henle are intra-renal compartments; solid arrows, flow of contrast; dashed arrows, flow of contrast-free fluid.

Adapted from cerebral perfusion, the Patlak-Rutland method has been applied for GFR calculations. This method is based on a two-compartment model, in which the outflow from the second, tubular compartment is ignored (Fig. 8B). In its traditional graphical implementation, the ratio of kidney \(K(t)\) to aortic concentration \(A_o(t)\) is plotted versus the ratio of the integral of \(A_o(t)\) to \(A_o(t)\). GFR is found as the slope of the linear regression to this curve and the vascular volume fraction as its intercept. Resulting GFR depends on the choice of the time interval used in computing the linear regression. In MR renography experiments on healthy volunteers and using slower contrast injections, Hackstein and colleagues\(^\text{61}\) found that GFR values determined from the interval of 30 to 90 seconds correlated best with reference measurements. This interval coincides with the uptake of contrast by the renal tubules in a normal kidney (see Fig. 1). The correlation of Patlak-Rutland GFRs with the reference improved considerably at higher contrast doses and reached \(r = 0.83\) at 16 mL of Gd-DTPA (in commercially available 500-mM dilution). This finding suggests that the Patlak-Rutland method may not be optimal for low-dose MR renography experiments or for protocols that provide a lower number of acquisitions within the tubular uptake interval.

Buckley and colleagues\(^\text{17}\) compared GFRs estimated with the Patlak-Rutland method and its extension, a two-compartment model (inspired by the widely used cancer perfusion models\(^\text{62}\)) in which the outflow from the tubules is accounted for (Fig. 8C). Both methods were applied to 35 patients with atherosclerotic renovascular disease. Dynamic three-dimensional images were acquired with gradient recalled echo sequence during free breathing at 4.5-second temporal resolution for up to 3.5 minutes. Data were extracted from a region of interest drawn around the kidney parenchyma on a single mid-coronal slice. Arterial input was measured in the abdominal aorta. Single-kidney GFR values obtained by both methods correlated significantly with the reference GFRs measured by \(^{51}\text{Cr-EDTA} \) clearance and renal scintigraphy; Spearman correlation coefficient was \(\rho = 0.81\) for Patlak-Rutland and \(\rho = 0.71\) for the extended model. The extended model overestimated GFR by almost 100%, whereas the Patlak-Rutland method overestimated them by about 30%. Such overestimation may be caused by the use of a single mid-kidney slice, in which the volume fraction of medulla is higher than in peripheral slices. The subjects’ mean global reference GFR was only 35 mL/min, which suggests severely decreased renal function. In such patients, the kidney uptake is low and slow, and the interval of 3.5 minutes may not be sufficient to characterize the outflow from the tubules, which may cause unreliable fitting with the compartmental model.

Higher GFR values produced by a compartmental model relative to the Patlak-Rutland model were first observed by Annet and colleagues.\(^\text{20}\) Experimenting on rabbits, this group analyzed the cortical concentration curves with the Patlak-Rutland method and a two-compartment model that accounts for tubular outflow and the spread of the bolus in the renal vasculature (see Fig. 8C). Unlike Buckley and colleagues,\(^\text{17}\) GFR obtained from Annet’s model underestimated the reference GFR measured by \(^{51}\text{Cr-EDTA} \) clearance. The extended model correlated better with
reference GFRs \((r = 0.82)\) than the Patlak-Rutland method \((r = 0.74)\). The relationship between the two methods was similar to that found by Buckley and colleagues\(^{17}\) (ie, lower GFRs were obtained with the Patlak-Rutland method compared with the extended model). The latter is likely caused by neglecting the outflow in the Patlak-Rutland method.

Similar results were obtained by Sourbron and colleagues\(^{25}\) in 15 healthy volunteers, whose MR renography images were analyzed voxel-wise with both the Patlak-Rutland model and the two-compartment model similar to that of Annet and colleagues.\(^{20}\) Both cortical and whole-kidney perfusion and filtration flows were determined. In agreement with Annet and colleagues\(^{20}\) and Buckley and colleagues,\(^{17}\) the full inflow-outflow model applied to whole-kidney data provided higher rates of perfusion \((229 \text{ mL/min/100 mL})\) and filtration \((31 \text{ mL/min/100 mL})\) than the Patlak-Rutland model \((210 \text{ mL/min/100 mL and 24 mL/min/100 mL, respectively})\). Cortical data provided higher perfusion, but lower filtration flow values \((340\text{ and 21 mL/min/100 mL with compartmental model}; 331\text{ and 15 mL/min/100 mL with the Patlak-Rutland model})\).

A three-compartment model proposed by the authors’ group\(^{5}\) makes use of separate cortical and medullary curves derived from segmented three-dimensional kidney images (Fig. 8D). Each tissue is thought to include the contributions from two compartments: a shared vascular compartment and a tubular compartment, proximal tubules in the cortex, and loops of Henle in the medulla. As in other renal models, the concentration in abdominal aorta provides the input function and is used to infer the concentration in the vascular compartment from which the contrast passes into the proximal tubules and then into the loops. Besides RPF and GFR, this model also yields cortical and medullary vascular volume fractions and fractions of contrast-free flow reabsorbed in proximal tubules and loops. Applied to three-dimensional MR renography data of 10 patients (20 kidneys) imaged using three-dimensional FLASH \((\text{TR/TE/FD} = 2.84/1.05/12 \text{ degrees})\), the model produced GFRs in good correlation with the reference measurements from \(^{99}\text{Tc-DTPA}\) clearance and scintigraphy \((r = 0.84; \text{ or } r = 0.93 \text{ without one outlier kidney with multiple renal cysts})\) and a slight underestimation of GFR. As estimated by Monte Carlo simulations, for 5% concentration noise, the errors in RPF and GFR were approximately 10% and 5%, respectively, for a well-functioning kidney, and slightly lower for a dysfunctional kidney. The errors were below 12% for vascular volumes, but much higher in reabsorbed fractions (23%–30% in healthy case and over 300% in dysfunctional kidney). The model was also shown to provide robust estimates of GFR for different widths of aortic inputs.

To account for noninstantaneous mixing of contrast, Zhang and colleagues extended this model by considering a minimum transit time that is required for tracer to traverse each compartment into a model based on the same arrangement of compartments as the previous model (see Fig. 8D).\(^{63}\) The model provides seven free parameters, including RPF, GFR, minimum transit times, and MTTs. Zhang’s model yields significantly better curve fits: the average relative root mean square error was 11.6% versus 15.5% obtained by the model of Lee and colleagues.\(^{5}\) Importantly, the model of Zhang and colleagues\(^{65}\) provided substantially more reliable fitting of the data from dysfunctional kidneys (Fig. 9). Despite the higher number of parameters, their stability in the presence of the data noise was also improved, with errors in both RPF and GFR lower than 3% for both well-functioning and diseased kidneys. There was a good correlation of model-derived GFRs against radionuclide measurements \((r = 0.82; \text{ or } r = 0.92 \text{ without the outlier kidney})\) similar to that obtained with Lee and colleagues\(^{5}\) model, although the GFR values were more strongly underestimated (on average by 41% versus 34% by Lee and colleagues\(^{5}\) model) (Fig. 10).

Glomerular Filtration Rate Quantification from Clearance Measurements

Choyke and colleagues\(^{1}\) compared GFR measured from clearance of \(^{99}\text{Tc-DTPA}\) \((\text{GFR}_{\text{Tc}})\) with GFR determined from clearance of Gd-DTPA \((\text{GFR}_{\text{Gd}})\) in 90 patients based on three urine and blood samples calculated using the standard clearance equation

\[
\text{GFR}_{\text{contrast}} = \frac{F \cdot U}{P} \quad (6)
\]

where F is the urine flow rate, and U and P are the concentrations of contrast in urine and plasma, respectively. The concentrations of Gd-DTPA in urine and plasma were determined by measurements of the T1 values of both fluids using nuclear MR spectrometer and an experimentally derived relationship to convert T1 into Gd-DTPA concentration. The correlation of \(\text{GFR}_{\text{Gd}}\) and \(\text{GFR}_{\text{Tc}}\) was high \((r = 0.94)\) and the coefficient of variation of their differences was only 3.6%. A similar study was performed by Ros and colleagues\(^{2}\) to determine GFR from plasma clearance of Gd-DTPA with MR angiography and MR renography. Again, the correlation between \(\text{GFR}_{\text{Gd}}\) and \(\text{GFR}_{\text{Tc}}\) was...
found to be high ($r = 0.98$) and the standard error was 3.85 mL/min.

Boss and colleagues measured GFR by capturing the clearance of gadobutrol from kidney and liver tissues of healthy volunteers over a long period of time (70 minutes) using a navigator-gated turbo-FLASH sequence. The rate of exponential decrease of MR imaging signal intensity with time is equal to the ratio of GFR and extracellular fluid volume, with the latter estimated from the weight and height of the subjects. The best estimates of GFR were obtained from measurements between 40 and 65 minutes after the injection of contrast, as compared with the simultaneous measurements of iopromide clearance from plasma, and were found to be within $5.9 \pm 14.6$ mL/min from the reference values. The mean half-life time of gadobutrol in renal cortex was found to be $92.6 \pm 23.7$ minutes. This approach to measurements of GFR has a number of limitations, such as the long imaging time and resulting susceptibility to motion artifacts, the reliance on the subject’s height and weight to estimate the extracellular fluid volume, and inability to provide the differential renal function.

Fig. 9. Gadolinium residue (mass) in the cortex and medulla of a functioning kidney (A) and a diseased kidney (B) fitted by the three-compartment model of Zhang and colleagues. Cortical and medullary residues are considerably lower in diseased kidney (B) than in the functioning kidney (A), but Zhang’s model provides good curve fits in both cases. (Adapted from Zhang JL, Rusinek H, Bokacheva L, et al. Functional assessment of the kidney from MR and CT renography: impulse retention approach to a multicompartment model. Magn Reson Med 2008;59:278–88; with permission.)

Fig. 10. Single-kidney GFRs obtained from the same data using models of Lee and colleagues (A) and Zhang and colleagues (B) versus the GFR values from the same-day nuclear medicine measurements. Both models underestimate GFR, especially Zhang’s model, but provide comparable correlations with radionuclide measurements. The linear regressions ($dashed lines$) are $y = 0.76x - 1.14$ ($r = 0.84$) (A) and $y = 0.61x - 0.32$ ($r = 0.82$) (B). Solid lines are the identity lines.
LIMITATIONS AND FUTURE DIRECTIONS

MR renography suffers from several limitations. One fundamental limitation of MR renography is the decrease of signal-to-noise ratio with decreasing kidney function, because the uptake of contrast in diseased kidneys is reduced compared with normal kidneys. MR renography studies of diseased kidneys may not be able to provide as much information as those of well-functioning kidneys. Determination of physiologic parameters from MR renography data requires several steps, including acquisition, image analysis, signal-to-concentration conversion, and tracer kinetic modeling. Each of these steps may contribute errors to the final results. Currently, there is no agreement regarding the best acquisition and analysis schemes. The tools for image analysis of dynamic data must be improved. Tracer kinetic models for analysis of renal data provide varying results despite many shared assumptions and these variations have not been reconciled. Most tracer kinetic models require measurements of arterial input function, which requires acquisitions with high temporal resolution and may suffer from inflow artifacts. Studies verifying MR renography–derived kidney parameters against reference measurements are scarce.

Future work includes overcoming these challenges and designing optimal protocols and tools for comprehensive analysis of MR renography data, including coregistration, segmentation, and voxel-based modeling. Shared solutions to these challenges may pave the way for multicenter studies to validate MR renography and establish its use in the clinical setting.

SUMMARY

Quantitative evaluation of renal function, most importantly perfusion and filtration, is often required for diagnosis and monitoring of vascular diseases, hypertension, obesity, diabetes, renal transplantation, and obstruction of the urinary tract. In research settings, MR renography has been shown to provide excellent anatomic detail and functional information in a single examination. MR renography has been researched since the late 1990s and particularly actively in the past few years when the imaging technology has matured to provide dynamic acquisitions with adequate spatial resolution and temporal resolution of a few seconds. Numerous studies reported measurements of renal perfusion and filtration with promising results. The results tend to vary greatly among groups and are difficult to compare because there is little agreement regarding the optimal experimental technique. Also in need of improvement are the image analysis tools for post-processing of large dynamic datasets. Greater understanding of the analytic methods, such as tracer kinetic models, is essential, as are the validation studies comparing the MR renography–derived functional parameters with those determined by established measurement techniques. Nevertheless, recent developments in MR renography are highly encouraging and it is hoped will lead to a consensus methodology. The implementation of MR renography in clinical practice has been hindered, however, because of the recently established connection between exposure to gadolinium contrast agents and developing nephrogenic systemic fibrosis in patients with renal insufficiency. Such patients may be evaluated using MR renography enhanced with macrocyclic contrast agents or by contrast-free methods, such as arterial spin labeling and blood oxygenation level dependent imaging.

With the development of reliable methods, MR imaging can become a one-stop modality that combines morphologic assessment with quantitative functional measures. Although further research is clearly needed to develop a clinically useful strategy, MR renography has the potential to become the leading diagnostic method for renal disease.

REFERENCES

6. Knopp MV, Balzer T, Esser M, et al. Assessment of utilization and pharmacovigilance based on spontaneous adverse event reporting of gadopentetate dimeglumine as a magnetic resonance contrast...


