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Combined Renal MRA and Perfusion with a Single Dose of Contrast

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Abstract

Both anatomical and functional scans are often performed when diagnosing renovascular diseases, which in many cases require two separate contrast injections. With nephrogenic systemic fibrosis (NSF) being associated with gadolinium, minimizing contrast injection dosage is desirable. In this study, a technique which performs time-resolved renal MRA and perfusion with a single scan and single dose of contrast has been evaluated in six healthy volunteers. A previously developed 3D MRA technique called Contrast-enhanced Angiography with Multi-Echo and Radial k -space (CAMERA) has been used to acquire images, and perfusion analysis was performed using deconvolution methods. Time-resolved MRA, as well as renal blood flow (RBF), renal volume of distribution (RVD), and mean transit time (MTT) maps were acquired.

Keywords

renal MRA; perfusion; time-resolved; single-dose

Introduction

Comprehensive assessment and diagnosis of patients with renovascular disease requires both anatomical and functional imaging. The use of Gadolinium-DTPA in time-resolved magnetic resonance angiography (MRA) is a promising tool for assessment of normal and compromised kidneys. Time-resolved renal MRA^{1–3} and renal perfusion^{4–10} are by themselves active areas of research, and often they are performed back to back during a renal exam.

In particular, there have been successful attempts to quantify renal perfusion using dynamic contrast-enhanced (DCE) methods which have been shown to be feasible^{4–10}. However, previous studies acquired only a single slice of the kidney or several thick slices in order to have sufficient temporal resolution for perfusion analysis. In addition, an angiogram of the renal arteries required a separate scan with an additional injection of contrast agent. With nephrogenic systemic fibrosis (NSF) being correlated with Gd-based contrast agents in patients with renal failure, it is critical that injection doses be kept to a minimum.

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In this study, we demonstrate the feasibility of using a previously developed 3D MRA technique called Contrast-enhanced Angiography with Multi-Echo and Radial k -space (CAMERA)¹¹ to obtain angiographic information in the renal vessels as well as perfusion information in the renal parenchyma with only one dose of contrast agent. The CAMERA sequence achieves this by utilizing sliding window reconstruction, which not only allows sub-second image updates for dynamic bolus depiction and perfusion analysis but also reduces sensitive to respiratory motion and contrast-bolus modulation.

Methods

Deconvolution Analysis

To a degree, some information about renal perfusion can be obtained by graphically observing the maximum signal enhancement and/or the rate of signal enhancement of the renal parenchyma. However, this technique does not take into account the shape of the arterial input function (AIF), which depends on the amount of contrast, injection rate, cardiac function, dispersion, and recirculation. As a result, the perfusion values are only semi-quantitative, although this information may be useful in quickly assessing unilateral renal diseases⁸.

To measure perfusion independent of injection rate, cardiac function, dispersion, and recirculation, the kinetics of a physiological tracer can be modeled using the following system

$$C = AIF \otimes IRF \quad [1]$$

where C is the concentration of the tracer in a region of interest (ROI) of the tissue over time, and IRF is the impulse response of that tissue. Since AIF and C are measured, IRF can be obtained by deconvolving C with AIF . The IRF that is obtained describes the perfusion characteristics of the tissue of interest independent of the magnitude and shape of the AIF .

There are several different ways to deconvolve Eq. [1]. The easiest and the most intuitive approach uses inverse Fourier transforms; however Fourier techniques are sensitive to noise¹⁴. Another general approach is the linear algebraic method. For discrete signals, Eq. [1] can be expressed in the following matrix form¹⁵:

$$\begin{pmatrix} C(t_1) \\ C(t_2) \\ \dots \\ C(t_N) \end{pmatrix} = \Delta t \cdot \begin{pmatrix} AIF(t_1) & 0 & \dots & 0 \\ AIF(t_2) & AIF(t_1) & \dots & 0 \\ \dots & \dots & \dots & \dots \\ AIF(t_N) & AIF(t_{N-1}) & \dots & AIF(t_1) \end{pmatrix} \cdot \begin{pmatrix} IRF(t_1) \\ IRF(t_2) \\ \dots \\ IRF(t_N) \end{pmatrix}. \quad [2]$$

The IRF vector can be obtained by linear algebraic methods such as regularization and singular value decomposition (SVD). Investigators have found that the SVD approach is relatively less sensitive to noise and results in accurate calculations¹⁵. A more detailed discussion on the accuracy of deconvolution methods can be found through other sources^{14–17}.

After the IRF is obtained, the perfusion parameters renal blood flow (RBF), renal volume of distribution (RVD) and mean transit time (MTT) are calculated as the following⁷:

$$\begin{aligned} \text{RBF} &\equiv \frac{1}{k_v} \max(\text{IRF}) \\ \text{RVD} &\equiv \frac{1}{k_v} \int_0^{\infty} \text{IRF}(t) dt \\ \text{MTT} &= \frac{\text{RVD}}{\text{RBF}}. \end{aligned} \quad [3]$$

where $1/k_v$ is a correction applied at the vascular inlet and used to adjust for filtration, water resorption, and secretion with k_v set to 1.36^{16} . The units of RBF, RVD, and MTT are ml/100g/min (ml of blood per 100g of tissue per min), ml/100g, and seconds. For RBF and RVD values, a tissue density of 1.04g/ml was used⁵. The RVD and RBF values were also multiplied by a constant $k_H=0.73$ which is commonly used to adjust for differences in arterial and capillary hematocrit¹⁶.

MR Acquisition

In this feasibility study, the CAMERA sequence was evaluated for renal MRA and perfusion in a small number of healthy volunteers. With institutional review board approval, six healthy volunteers were scanned with the protocol. A single dose (0.1 mmol/kg) of Magnevist (Berlex, Wayne, NJ) was injected for each study. All images were acquired on a Siemens Trio 3T scanner (Siemens AG, Erlangen, Germany) using a phased array body coil.

The CAMERA sequence, a radial 3D spoiled gradient echo with multi-echo in the partition direction and sliding mask subtraction, was used to acquire the data in the coronal plane. The following imaging parameters were used: echo train length (ETL) = 4, number of projection (N_p) = 192, readout points (N_{RO}) = 192, 75% fractional echo, FOV = 240mm × 240mm, slices = 32, slice thickness = 3.0 mm, flip angle = 30°, TR = 6.02ms, and TEs = 1.45, 2.48, 3.51, 4.54 ms. During image reconstruction, magnitude subtraction images are generated by subtracting each measured volume by the volume acquired prior to it. In a static mask subtraction, the subtracted volume is the initial acquisition. The sliding mask technique, which has been previously described in Cashen et al¹², is a method for improving the separation of arterial and venous phases by subtracting each acquired volume by the volume acquired a fixed amount of time prior. This process approximates the time-derivation of the signal-time curve at each pixel and as such, is better suited than static subtraction for imaging that may involve subject movement.

The scans were performed with a 2-part breath hold technique. The subject held his/her breath for the first repetition (~9.5 seconds), which served as the first pre-contrast subtraction mask. Following a short break (15 seconds), the remaining 4 consecutive repetitions were acquired with the subject holding his or her breath for as long as possible (~36–40 seconds). The subjects were observed during the course of the imaging to ensure compliance with the breath hold protocol. This breath hold protocol was successfully used in the evaluation of patients with pulmonary arterial hypertension¹⁸. A single dose of contrast agent was injected at 4ml/s followed by 20ml of saline at 4ml/s, at the beginning of the second breath hold.

Image Reconstruction

The images were reconstructed online on the scanner with a sliding window factor of 16, resulting in frame rates of approximately 558ms/frame, or 1.7 frames/sec. There were a total of 5 repetitions producing 81 time points, with the first 16 time points corresponding to the mask measurement and final 65 time points corresponding to the dynamic measurements. Full 3D volumes of 32 slices were obtained for each frame and coronal maximum intensity projections (MIPs) were obtained for perfusion analysis and angiography, respectively.

Tracer Kinetics

The 3D CAMERA technique utilizes a larger temporal sampling window (~9.5 seconds) for measuring the bolus signal than typical 2D multi-echo EPI sequences. It is well known that the length of the acquisition influences the shape of the bolus profile and may potentially distort perfusion measurements during SVD calculation of the IRF. We performed Monte Carlo simulations to determine the error in the IRF induced by this larger sampling window measurement of the AIF and tissue contrast curves.

A representative AIF was chosen from the volunteer data and fitted to a gamma variate function. The known IRF was based on the single-exponential model¹⁷ using MTT values ranging from 5 to 25 seconds. The tissue curve was generated by convolving the known AIF and IRF and adding Gaussian noise to reduce the signal-to-noise ratio (SNR) to ~30. This is the SNR of a typical renal angiogram acquired through the CAMERA sequence. We then re-sampled the AIF and tissue curves with increasing acquisition windows by convolving each with different length *rect* functions as shown in Eq. [4].

$$\text{rect} \otimes C = \text{rect} \otimes \text{AIF} \otimes \text{IRF} \quad [4]$$

Applying SVD to Eq. [4] then allowed us to re-calculate the IRF which was subsequently fitted to the single-exponential model and used to determine the MTT parameter, MTT_{Fit} . The error was calculated as the percent difference between the true and fitted values.

In Vivo Signal to [Contrast Agent] Conversion

C and AIF have units of tracer concentration (e.g. mM), which must be calculated from the CAMERA signal intensity. This calibration must be performed for each scan because the signal intensity depends on many factors such as imaging protocol, receiver coil sensitivity, and position. In addition, different sequences will have different contrast mechanisms. For example, a T1-weighted sequence will have brighter signal for higher Gadolinium-contrast agent concentrations while a T2 or T2*-weighted sequence will have darker signal. The steady-state signal intensity of small flip angle spoiled gradient echo sequences (like CAMERA) with short TR and TEs is mainly T1 weighted. For ultra-short T1s (<100ms), T2 effects become more pronounced; however we hypothesized that for physiological concentrations of contrast-agent in the human body, we may be able to obtain a simple calibration between T1 and CAMERA signal intensity. This calibration was determined empirically in the phantom study described below.

T1 values for known concentrations were measured. 9 vials filled with solutions of 0.039, 0.078, 0.156, 0.313, 0.625, 1.25, 2.5, 5, and 10mM of contrast agent (Magnevist) and one vial with 1% saline in water were imaged with an inversion recovery gradient echo (IR-GRE) sequence to determine the T1 values of the solutions containing different Magnevist concentrations. Inversion times (TIs) 30, 100, 200, 300, 500, 1000, 2000, 4000 ms were used to find the T1 values by fitting the TI and signal values to the equation: $S = S_0(1 - 2\exp(-TI/T1))$.

After obtaining the T1 values, the same vials of contrast agent were imaged with the CAMERA sequence using an identical protocol to that described in the MR acquisition section. Signal from the MRA sequence was plotted against the previously measured T1. For the sequence used for this study, a simple linear fit resulted in a function that converts the signal intensity (SI) to 1/T1 with R^2 of 0.999 (Figure 1). Then, the concentration of Magnevist [Mg] can be calculated by solving the equation:

$$\frac{1}{T1_{Mg}} = \frac{1}{T1_{pre}} + [Mg] \cdot R1 \quad [5]$$

using the R1 value of $4.9 \text{ s}^{-1}\text{mM}^{-1}$ obtained from the manufacturer.

Additionally, a constant multiplier was derived for each scan to adjust the coil sensitivity and receiver gain for each exam. Blood in the aorta was assumed to have a T1 of 1300ms, which results in a signal intensity of approximately 56 from the fitted equation (Figure 1). Then, for each exam, all the signals were scaled so that the pre-contrast signal in the aorta was 56.

It should be noted that for linear SI to concentration conversion, substitution of values into Eq [5] results in a constant multiplier that simply scales both the arterial and tissue contrast agent concentration value by a constant. This value has no net effect on the perfusion value, if it is assumed to be constant for different tissue types, since it is canceled during deconvolution. Therefore, for sequences that produce linear 1/T1 to contrast agent concentration calibration curves, the conversion is unnecessary.

Perfusion Analysis

Perfusion analysis was performed offline using MATLAB (Mathworks, Natick, MA). The arterial input function (AIF) was obtained by drawing a circular ROI over the aorta close to the renal arteries. $T1_{pre}$ was obtained by drawing an ROI on an image before the arrival of contrast for either the aorta (blood) or renal tissue. The corresponding value was then scaled to 56 in the aorta as explained in the previous section. This constant multiplier was applied to all signal intensity values. Signal intensity for the AIF and tissue concentration curves were then converted into 1/T1 values using the relationship found in Figure 1.

Then, contrast agent concentration for each voxel of the renal parenchyma, was calculated for each time point to obtain C(t). C(t) was deconvolved using SVD with $w_{ij}=0.2$ to obtain the IRF. Perfusion parameters (RBF, RVD, and MTT) were obtained using Eq. [3]. The perfusion analysis process is illustrated in Figure 2. To obtain mean perfusion values, ROIs were placed to cover the whole cortex for each slice that included the renal parenchyma.

Results

The results of our Monte Carlo simulations are shown in Figure 3. We found that sampling windows of up to 9.5 seconds (the duration of each CAMERA volumetric acquisition) could be utilized while maintaining a less than 5% error in the fitted MTT parameter of the recalculated IRF.

The MRA images and perfusion maps were successfully acquired for 5 of the 6 volunteers. One of the six MRAs suffered from mild motion artifacts due to the inability of the volunteer to follow breath hold instructions. The MRA for the unsuccessful exam was of satisfactory quality because of the intrinsic ability of the time-resolved MR technique to image moving objects. However, the perfusion calculation required contrast uptake curves for each voxel and was not performed for the dataset with motion. Figure 4 shows 16 selected frames depicting bolus dynamics from a typical time-resolved renal MRA using the CAMERA technique. Sequential filling of the aorta, renal arteries, and segmental vessels can be seen, as well as enhancement of the renal parenchyma. The frame rate was approximately 1.7 frames/sec. In the figure, every other frame from the arterial and venous phases are shown.

Figure 5 shows the RBF, RVD, and MTT maps from the same exam. In each map, four slices were chosen from a set of 32 slices, and ROIs were placed to cover the entirety of the cortex. Mean RBF, RVD and MTT values were 228.6 ± 38.4 ml/100g/min, 49.3 ± 4.0 ml/100g, and 14.2 ± 2.0 sec in the cortex. The mean cortex/medulla RBF ratio was 3.8 ± 0.3 . Table 1 shows the results of our study for five volunteers. The cortical RBF value is underestimated and the RVD and MTT values were overestimated compared to the values found in physiology texts and relevant literature: RBF=380ml/100g/min, RVD=27ml/100g, MTT=4.4s. The ratio of cortical to medullary flow is in close agreement with the literature value of 4²⁰.

Discussion

The technique presented combines both time-resolved MRA and perfusion in a single sequence, which decreases acquisition time and contrast agent dose. The main features of this technique that make this possible are: 1) high frame rates and temporal samples due to CAMERA and sliding window reconstruction and 2) 3D coverage of the renal parenchyma.

The anatomic accuracy of the technique has been validated previously in the brain for fast flowing vascular malformations. In this study a similar technique was used not only to image anatomy but also measure renal function. Although an in-depth comparison with a standard of reference (e.g. microspheres) is required to verify the measured perfusion parameters, this technique has successfully produced reasonable measurements found in literature while providing a time-resolved MRA.

The utilization of a time-resolved MRA sequence to acquire functional information is based on tracer kinetics theory developed from nuclear medicine with Tc-99m DTPA. This theory has successfully been applied to MR imaging with gadolinium contrast agents^{22–24} because it has been shown that Tc-99m DTPA and Gd-DTPA have very similar kinetics. The tracer kinetics model calculates perfusion based on the ratio of maximal slopes of the time-integrated tissue and arterial contrast uptake curves. This model however assumes that the tracer curves are obtained with an infinitely small temporal sampling interval. Longer sampling intervals increase the width of the bolus profiles which in turn decrease the maximum slopes of time-integrated curves. For very fast 2D sequences, the effect of the sampling interval may be negligible. However, previous studies have determined that the shape of a contrast-time curve depends strongly on the sampling interval of a dynamic MR sequence.

Our technique utilizes a larger temporal acquisition window for measuring bolus signal than typical multi-echo EPI perfusion sequences. In addition, our use of sliding window reconstruction for increased image update rates has the known effect of low pass filtering temporal data. This could cause systematic underestimation of the bolus profile peaks and upslopes. Although further verification is necessary, our Monte Carlo simulations modeling the impact of larger sampling windows showed that deconvolution could mitigate these effects as they occur in both the arterial (AIF) and the tissue contrast curves. Nonetheless, such models should be carefully used. Appropriate utilization of acceleration techniques such as parallel imaging²⁸ or highly constrained projection reconstruction (HYPR)²⁹ could improve accurate measurement of the bolus profile by reducing the sampling interval.

In this study, underestimation of RBF and overestimation of RVD values were observed relative to values reported in literature⁶. However, our values for RBF fall within the range of those determined by other contrast and non-contrast MR perfusion quantification techniques elsewhere in literature, most notably Dujardin et al (115–154 ml/100g/min), Vallee et al (244 ml/100g/min)⁴, Karger et al (213ml/100g/min)³⁰, Martirosian et al (200–

280 ml/100g/min)³¹, Song et al (376 ml/100g/min)³², and Schoenberg et al (379 ml/100g/min)⁶. However these values are all underestimations of the values given in physiology texts, which report an average of 400 ml/100g/min in the kidney overall with medullary flow rates ranging from 23 ml/100g/min in the inner medulla to 230 ml/100g/min in the outer medulla³³. Our ratio of cortical RBF to medullary RBF of 3.8 is close to the literature value of 4.0²⁰.

It has been suggested that errors in the AIF may be a significant contributor to RBF underestimation in contrast MR perfusion techniques⁷. For example, flow-related enhancements during systole may cause overestimation of the AIF and subsequent underestimation in perfusion. A second possible source of error in our measurements may have been from bolus dispersion³⁴. Vascular abnormalities in between the tissue and the aorta, where the AIF is usually obtained, may cause the shape of the AIF to change before entering the renal tissue. Performing deconvolution with an AIF obtained from the aorta, which is different than the true AIF would result in an inaccurate impulse response function. Additionally, the deconvolution method itself is an ill-posed problem and is susceptible to computation errors¹⁵.

A good breath hold is critical for this technique since the images must be acquired continuously for the entire first pass of the contrast. As a result, there is no way to avoid the breath hold of approximately 30–40 seconds unless a motion correction is performed while images are taken during free breathing. However, it should be noted that this same protocol has been used successfully in thoracic imaging of patients with pulmonary arterial hypertension¹⁸. In our experience, with proper instruction and a practice run before the actual scan, most of the subjects can hold their breaths for the duration of the scan. In addition, calculated transit times of ~14-seconds indicate that although the total scan may exceed 35-seconds, the first pass of contrast (and thus the data used for perfusion calculation) occurs over a shorter period of time. As a result, images towards the end of the scan from subjects that fail the breath-hold duration may potentially be discarded without compromising calculation of perfusion.

The initial non-contrast image is acquired in a 10-second breathhold in the beginning of the scan prior to injection. Although misregistration of this volume from the remaining acquisition may cause issues for certain CE MRA techniques utilizing static mask-mode subtraction, the CAMERA technique we utilized mitigates this effect by using a sliding mask which dynamically updates the subtraction volume.

Other MR techniques to measure renal function exist, such as measuring the flow in renal arteries using phase contrast, which is related to perfusion. However respiratory motion and long imaging times³⁵, which can be prohibitive in many patients, may contribute a significant source of error. In addition, the image can only be acquired perpendicular to the vessel giving no information on vessel morphology and perfusion in the renal parenchyma⁸. Non MR techniques such as Doppler ultrasound can also be used, but they have been shown to have inferior performance to MRA³⁶. In conclusion, a combined MRA and perfusion measurement with a single MRA sequence was shown to be feasible, though the perfusion parameters require more rigorous validation.

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Figure 1.

Regression analysis determined a linear relationship between signal intensity (SI) from the CAMERA acquisition and $1/T1$ ($R^2=0.999$). Using this relationship, contrast agent concentration was computed and arterial and signal bolus curves were determined.

Figure 2. Illustration of post-processing perfusion analysis. An AIF was obtained as shown and deconvolved with tissue contrast agent concentration curves to obtain the tissue IRF on a voxel-by-voxel basis.

Figure 3.

A typical time-resolved renal MRA of a normal subject using the CAMERA sequence is shown. The frame rate was approximately 1.7 frames/sec allowing a large number of temporal samples for tissue and arterial contrast curves. For a typical scan duration of ~48 seconds, this produces 81 time points. Here, every other frame is displayed over a selected range of time points displaying arterial and venous phases.

Figure 4. Monte Carlo simulations predict the expected error in calculating MTT from the SVD deconvolution of the IRF when large sampling intervals are used to measure the AIF and tissue contrast curves. The error in MTT from a 9.5 second sampling window (the duration of 1 CAMERA volumetric acquisition) is < 5%.

Figure 5. Representative RBF, RVD, and MTT maps of a normal volunteer are shown. Each map displays 3 selected slices from a total of 32 slices.

Table 1

Calculated cortical RBF, RVD, and MTT in five healthy volunteers

Subject	RBF (ml/100g/min)	RVD (ml/100g)	MTT (s)
1	203.9 ± 50.4	46.8 ± 6.9	14.2 ± 2.1
2	276.8 ± 90.1	52.5 ± 10.2	12.4 ± 4.1
3	195.8 ± 57.3	53.9 ± 11.1	17.3 ± 3.7
4	202.7 ± 43.8	44.1 ± 16.1	14.2 ± 2.4
5	263.8 ± 55.5	49.0 ± 10.1	12.8 ± 2.8
Mean	228.6 ± 38.4	49.3 ± 4.0	14.2 ± 1.9