HHS Public Access

Author manuscript

Acad Radiol. Author manuscript; available in PMC 2016 May 04.

Published in final edited form as:

Acad Radiol. 2016 March ; 23(3): 368–373. doi:10.1016/j.acra.2015.10.021.

MR Angiography of Renal Transplant Vasculature with Ferumoxytol: Comparison of High-Resolution Steady-State and First-Pass Acquisitions

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Abstract

Rationale and Objectives—This work aimed to quantify the differences in signal-to-noise ratio (SNR) and vessel sharpness between steady-state and first-pass magnetic resonance angiography (MRA) with ferumoxytol in renal transplant recipients.

Materials and Methods—We performed a retrospective study of adult patients who underwent steady-state and first-pass MRA with ferumoxytol to evaluate renal transplant vasculature. SNR was calculated in the external iliac artery, and vessel sharpness was calculated in the external iliac and renal transplant arteries for both acquisitions. Data were compared using Student's *t* test.

Results—Fifteen patients were included (mean age 56.9 years, 10 males). The mean SNR of the external iliac artery was 42.2 (SD, 11.9) for the first-pass MRA and 41.8 (SD, 9.7) for the steady-state MRA ($p = 0.92$). The mean vessel sharpness was significantly higher for the steady-state MRA compared to first-pass MRA for both external iliac (1.24 vs. 0.80 mm^{-1}, $p < 0.01$) and renal transplant arteries (1.26 vs. 0.79 mm^{-1}, $p < 0.01$).

Conclusion—Steady-state MRA using ferumoxytol improves vessel sharpness while maintaining equivalent SNR compared to conventional first-pass MRA in renal transplant patients.

Keywords

Steady state; MRA; ferumoxytol; renal transplant; nephrotoxicity; contrast

INTRODUCTION

Ferumoxytol is an ultra-small superparamagnetic iron oxide agent used to treat iron-deficiency anemia in patients with renal insufficiency. It causes T1-shortening, and there has been recent interest in its use as a magnetic resonance imaging (MRI) contrast agent (1). A major advantage of ferumoxytol is its ability to be administered to patients with renal failure. As it is not gadolinium based, there is no risk of nephrogenic systemic fibrosis (NSF). Patients with renal transplants are in a unique position to benefit from this agent. In the setting of graft dysfunction, anatomic imaging of the renal transplant vasculature is often needed to evaluate for transplant renal artery stenosis when ultrasound (US) is inconclusive

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or intervention is being planned (2). However, MRI with gadolinium-based contrast agents (GBCAs) and contrast-enhanced computed tomography (CT) are limited by the risks of NSF and contrast-induced nephropathy, respectively.

Ferumoxytol has been preliminarily shown to be useful in evaluating renal transplant arteries in patients with graft dysfunction (3). This agent is particularly suited for magnetic resonance angiography (MRA) because it initially acts as a blood pool agent that remains in the intravascular space for a prolonged period of time. This allows for steady-state MRA (SS-MRA) to be performed, using prolonged acquisitions that improve signal-to-noise ratio (SNR) and subsequently the potential for improved spatial resolution (4). In contrast, conventional extracellular GBCAs diffuse into the extravascular space and are rapidly excreted by the kidneys. The intravascular concentration of conventional GBCAs decreases soon after injection, and therefore, MRA is reliant on first-pass arterial phase imaging which limits acquisition time and thus SNR and spatial resolution. Therefore, there is potential for an improvement in image quality using SS-MRA with ferumoxytol compared to conventional first-pass MRA. The purpose of this study is to describe an imaging protocol for SS-MRA with ferumoxytol, and quantify the differences in SNR and vessel sharpness between SS-MRA and first-pass MRA in renal transplant recipients.

MATERIALS AND METHODS

Patient Population

This Health Insurance Portability and Accountability Act compliant study was approved by the Institutional Review Board, and the requirement for informed consent was waived because of its retrospective nature. A search of our single institution radiology database was performed to identify patients greater than 18 years of age with single renal transplants who had undergone MRA with ferumoxytol including first-pass and SS-MRA as part of their clinical care to further evaluate renal artery stenosis seen on prior US, and to aid in the planning of angiography. Fifteen cases were identified and included. As this was an off-label use of the drug, informed consent was obtained in all patients before undergoing MRA.

MRI Technique

All patients were instructed to fast for 4 hours before MRI examination. Images were acquired on a 1.5 Tesla General Electric Signa HDxt MRI Scanner system (GE Medical Systems, Milwaukee, WI, USA), with a phased array torso coil. MRA was performed using a 3-D, T1-weighted spoiled gradient echo pulse sequence with elliptical centric k-space filling. The dose of ferumoxytol was determined by the following formula: weight of patient (kg) × (3 mg iron/kg) × (17 mL ferumoxytol vial/510 mg iron) = mL to be injected intravenously. It was injected at a rate of 2 mL/s followed by 20 mL of normal saline at a rate of 2 mL/s. The patients' blood pressure and pulse were recorded before and after the administration of ferumoxytol to evaluate for any evidence of hypotension. The first-pass MRA was timed using magnetic resonance fluoroscopy, and the acquisition was initiated when contrast first arrived in the abdominal aorta. The SS-MRA was prescribed using the first-pass MRA images as a localizer, and the acquisition began approximately 1 minute after completion of the first-pass MRA. Both sequences were performed during free

breathing and acquired in the coronal plane. The SS-MRA was also acquired in an oblique plane along the long axis of the transplant renal artery as deemed appropriate by the supervising radiologist. All measurements were taken from the coronal sequences. The imaging parameters for the first-pass and SS-MRA acquisitions are listed in Table 1.

Image Analysis

Images were analyzed by one board certified radiologist (M.C.) with subspecialty training in abdominal imaging who was blinded to clinical information and other imaging studies. The methods for measuring SNR and edge sharpness were reviewed with a radiology physicist (AC) before data abstraction to ensure proper technique. SNR was calculated by placing a region of interest (ROI) in the center of the lumen of the external iliac artery at the level of the renal transplant artery anastomosis. Care was taken to avoid the edge of the vessel and place the ROI in the same anatomical location for both sequences. Six ROIs of the same size were placed in the bladder lumen to determine the background standard deviation. The bladder was chosen for the background as the small field of view for the steady-state sequence excluded any regions outside of the patient, and the bladder consistently had no signal beyond noise similar to background outside the patient on the first-pass acquisition. SNR was calculated using the following formula:

$$SNR = S / \sigma_{tot}$$

where S is the mean signal intensity in the iliac artery and σ_{tot} is the background standard deviation calculated from the six background ROIs using

$$\sigma_{tot} = \sqrt{\left(\frac{1}{6}\right)(\sigma_1 2 + \sigma_2 2 + \ldots + \sigma_6 2)}$$

Vessel edge sharpness was calculated using the 20–80% rise distance (d) determined from line-intensity profiles drawn perpendicular to the vessel (Fig 1). Vessel edge sharpness was calculated as 1/d. This was determined for the external iliac artery and renal transplant artery, using care to draw the line at the same vessel location for both sequences. If there were multiple transplant arteries, the larger was used.

Statistical Analysis

SNR was compared between the first-pass and SS-MRA using a two-tailed paired *t* test. Vessel edge sharpness was compared using a one-tailed paired *t* test. For the latter, we tested if the iliac and renal arteries have a higher sharpness when using SS-MRA versus first-pass MRA. A one-tailed *t* test was therefore deemed appropriate.

RESULTS

Fifteen patients were included (mean age 56.9 years, 10 males). The transplant was in the right lower quadrant in 14 patients and in the left lower quadrant in 1. All transplant renal

arteries were anastomosed to the external iliac artery. The transplant renal artery was single in 11 patients and double in 4. No adverse reactions to ferumoxytol were observed in any patients.

The mean SNR of the external iliac artery was 42.2 (SD, 11.9) for the first-pass MRA and 41.8 (SD, 9.7) for the SS-MRA ($p = 0.92$). The mean vessel sharpness was significantly higher for the SS-MRA compared to first-pass MRA for both external iliac and renal transplant arteries as shown in Table 2. Figure 2 demonstrates the full field of view images for first-pass and SS-MRA sequences in a patient with a normal transplant renal artery.

DISCUSSION

The results of our study show that high-resolution SS-MRA with ferumoxytol provides superior vessel sharpness with equivalent SNR to conventional first-pass MRA in renal transplant recipients.

Conventional first-pass MRA is limited by conflicting demands for high temporal resolution and high spatial resolution. Because conventional GBCAs diffuse rapidly out of the vascular space, high-resolution MRA is reliant on first-pass imaging. This creates the need to appropriately time the acquisition as well as limit the length of the acquisition. This results in restrictions on SNR and/or spatial resolution. The use of intravascular blood pool contrast agents permits steady-state imaging to be performed, allowing for acquisition times of several minutes leading to improved SNR and thus allowing for increased spatial resolution. SS-MRA with the blood pool GBCA Gadofosveset has been shown to be superior to first-pass imaging of the carotid arteries and of thoracic vasculature in children (5,6).

Like Gadofosveset, ferumoxytol is a blood pool agent allowing for SS-MRA to be performed. However, as it is not gadolinium based, it can be used in patients with renal failure without concerns for NSF and has been successfully used as an MRA contrast agent throughout the body (1,7). Therefore, this agent is of particular interest in the renal transplant population who often need vascular evaluation in the setting of renal dysfunction, which may preclude use of iodinated contrast in CT or GBCAs for MRA. Although US is the first-line imaging modality to evaluate renal transplant vasculature, it is highly operator dependent and may often be limited by patient body habitus and overlying bowel gas (8). Furthermore, the measurement of flow velocities used to determine arterial stenoses may vary with patient positioning and vessel tortuosity (9). US does not provide detailed anatomic images and MRA is useful to define the exact location and length of stenosis, and number and location of renal arteries, information that may be useful in planning angiography. US may also be limited in evaluating the small renal arteries in pediatric en-bloc renal transplants where only the donor aorta may be assessed, and there is often incomplete assessment of the iliac arteries which limits evaluation for inflow stenosis (2). Indeed, MRA with ferumoxytol has been shown to be of use in evaluating the renal transplant vasculature when US is non-diagnostic (3). It has also been successfully used to image arteriovenous fistulas in patients with renal dysfunction (10). High-resolution SS-MRA is of particular interest in renal transplant recipients as the transplant renal arteries—especially accessory arteries—can be very small in caliber, as small as 1 mm in diameter

(11). Therefore, high spatial resolution imaging may be needed to detect and quantify any arterial stenoses. The results of our study show that SS-MRA of renal transplant arteries with ferumoxytol improves vessel sharpness by over 50% compared to conventional first-pass imaging. At the same time, the SNR is maintained at a similar level.

SS-MRA with ferumoxytol also eliminates the requirement to accurately time the first-pass arterial phase acquisition which can be a source of technical failure during MRA. Because of the blood pool properties of ferumoxytol the acquisition can be made independent of timing. It also allows repeat imaging to be performed if one acquisition is degraded because of patient motion or other artifact. These acquisitions can also be performed in oblique planes that better align with and depict the transplant renal artery (Fig. 3). The higher resolution also allows for superior multi-planar and curved reformations to be made, given the near isotropic voxels (Fig. 4).

The long acquisition time could theoretically introduce more motion artifact; however, this did not lead to any reductions in image quality in our study. This is likely caused by, the relatively fixed position of the iliac and renal transplant arteries. Additionally, SS-MRA may also be complicated by venous contamination as both arteries and veins will enhance. However, the renal arteries can be easily identified by tracing their origin to the external iliac artery and this does not produce any significant limitation. Because of the extreme paramagnetic properties of ferumoxytol, high intravascular concentrations of the agent can cause artifacts because of signal loss, and care must be taken to inject a low enough concentration to avoid this pitfall (12). This artifact did not occur in our cases on either first-pass or SS-MRA supporting the use of the dose and injection protocol used in our study.

It should be noted that cases of severe hypotension and anaphylaxis have been reported after administration of ferumoxytol for therapeutic indications (13,14). The safety profile of ferumoxytol as an MRI contrast agent has not been fully studied, and it remains an off-label use of the agent.

Our results suggest that SS-MRA with ferumoxytol may obviate the need for first-pass imaging. This could have important implications for the administration of the agent and the imaging protocol. First, it would be possible to administer the agent while the patient is in the holding area, not in the scanner. This would make observation for any reaction much easier. Second, a slow injection rate could be used which also may minimize the risk of reactions. It would also eliminate the need to accurately time the arterial bolus which may improve technologist workflow. Such considerations warrant further study in the future.

Our study has limitations. We did not compare the accuracy of the two sequences to quantify arterial stenoses as we did not have a reference standard. Because of the retrospective nature of the study we were not able to assess a variety of sequence parameters to optimize the SS-MRA protocol. However, the lack of change in SNR between the two acquisitions suggests our protocol is appropriate to improve spatial resolution without negatively affecting other imaging parameters. We also did not compare SS-MRA to any non-contrast MRA techniques. These have also been shown to be viable techniques to image the transplant renal

arteries without the use of GBCAs, and future studies directly comparing the two techniques are warranted (15–17).

In conclusion, SS-MRA using ferumoxytol improves vessel sharpness while maintaining similar SNR compared to conventional first-pass MRA. This is a viable technique for evaluation of renal transplant vasculature in patients with renal dysfunction.

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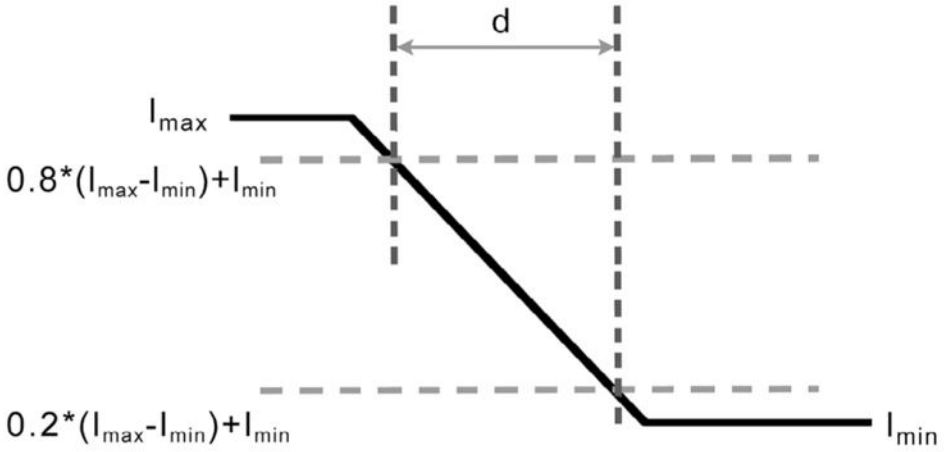

Figure 1.
Line intensity profile for calculating vessel sharpness.

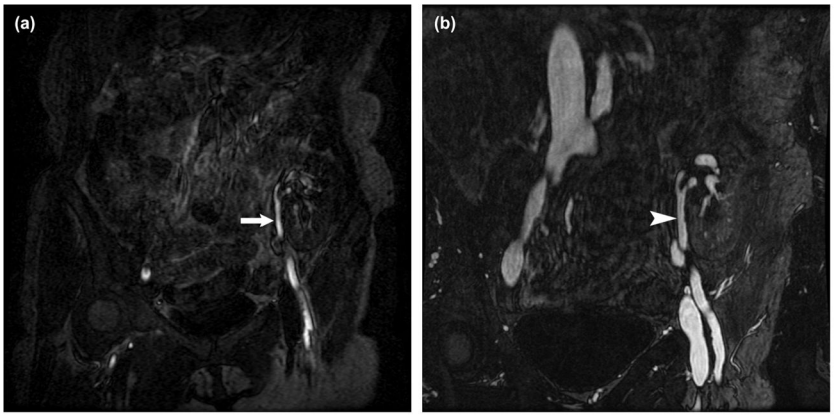

Figure 2.

(a) Full field of view coronal image from first-pass MRA reveals the transplant renal artery in the left lower quadrant (arrow). (b) Coronal image from the SS-MRA with a reduced field of view depicts improved vessel sharpness of the renal artery (arrowhead). MRA, magnetic resonance angiography; SS-MRA, steady-state MRA.

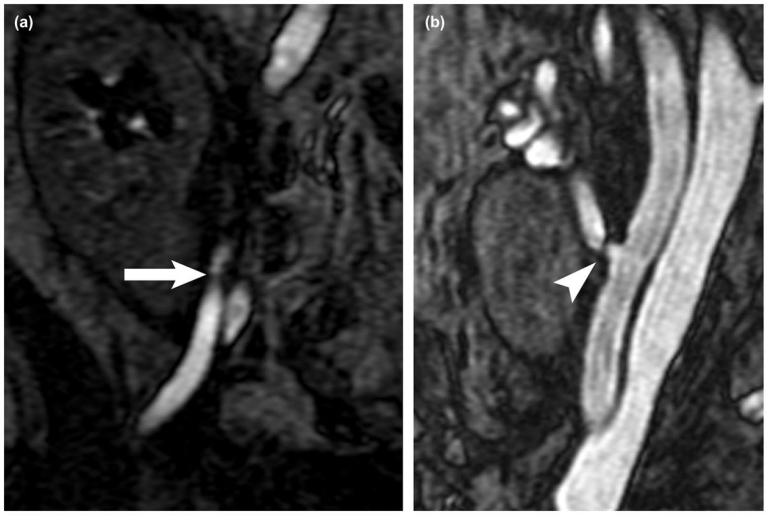

Figure 3.

(a) Coronal image from first-pass MRA shows stenosis of the proximal transplant renal artery (arrow), but it is difficult to assess the degree of narrowing as the vessel courses posteriorly out of the plane of imaging. (b) Coronal oblique SS-MRA prescribed along the long axis of the vessel more clearly shows the high-grade stenosis (arrowhead). MRA, magnetic resonance angiography; SS-MRA, steady-state MRA.

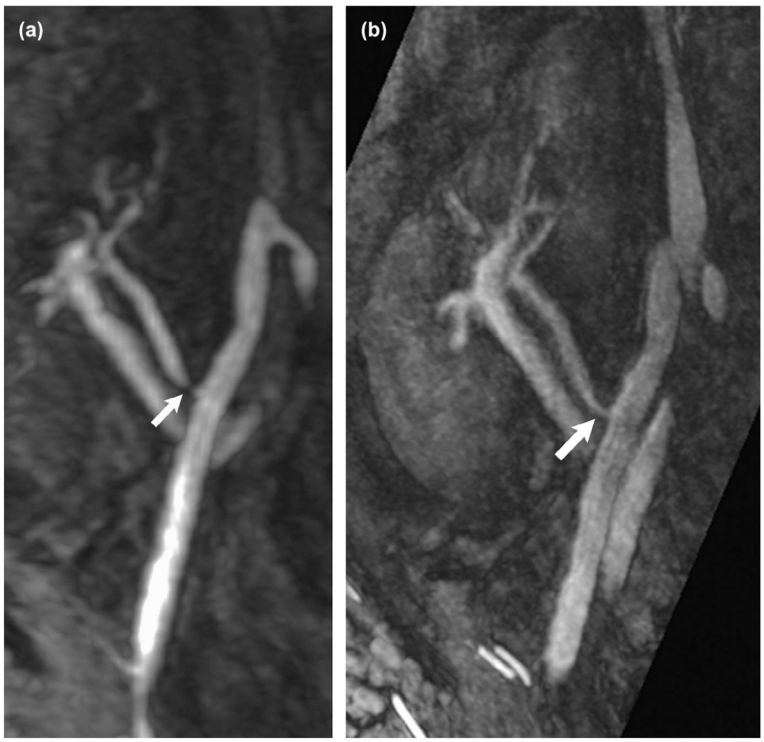

Figure 4.

(a) Multiplanar reformat maximum intensity projection image from first-pass MRA suggests near complete occlusion (arrow) of the proximal transplant renal artery. (b) Multiplanar reformat maximum intensity projection image from SS-MRA more clearly shows the residual vessel lumen at the stenosis (arrow) which was less severe (approximately 60%). MRA, magnetic resonance angiography; SS-MRA, steady-state MRA.

TABLE 1

Imaging Parameters for First-pass and Steady-state MRA Using Ferumoxytol

	First Pass	Steady State
Field of view	34 cm	26 cm
Matrix	320 × 192	384 × 256
Slice thickness	2.8 mm	1.6 mm
Spacing	1.4 mm	0.8 mm
Mean volume thickness	87 mm	77 mm
Voxel size	5.3 mm^3	1.1 mm^3
Nex	1	3
TE	1.6 ms	2.0 ms
TR	4.9 ms	6.1 ms
Flip angle	30	30
Imaging time	20 s	4.3 min

MRA, magnetic resonance angiography; TE, echo time; TR, repetition time.

TABLE 2

Mean Edge Sharpness in the External Iliac and Renal Transplant Arteries for First-pass and Steady-state MRA (Numbers in Parentheses are Standard Deviations)

	Edge sharpness (mm^{-1})		
Artery	**First Pass**	**Steady State**	**p-Value**
External iliac	0.80 (0.14)	1.22 (0.23)	<.01
Renal transplant	0.79 (0.15)	1.26 (0.17)	<.01

MRA, magnetic resonance angiography.