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MINIREVIEWS

Functional assessment of transplanted kidneys with magnetic resonance imaging

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Abstract

Kidney transplantation has emerged as the treatment of

choice for many patients with end-stage renal disease, which is a significant cause of morbidity and mortality. Given the shortage of clinically available donor kidneys and the significant incidence of allograft dysfunction, a noninvasive and accurate assessment of the allograft renal function is critical for postoperative management. Prompt diagnosis of graft dysfunction facilitates clinical intervention of kidneys with salvageable function. New advances in magnetic resonance imaging (MRI) technology have enabled the calculation of various renal parameters that were previously not feasible to measure noninvasively. Diffusion-weighted imaging provides information on renal diffusion and perfusion simultaneously, with quantification by the apparent diffusion coefficient, the decrease of which reflects renal function impairment. Diffusion-tensor imaging accounts for the directionality of molecular motion and measures fractional anisotropy of the kidneys. Blood oxygen level-dependent MR evaluates intrarenal oxygen bioavailability, generating the parameter of R2* (reflecting the concentration of deoxyhemoglobin). A decrease in R2* could happen during acute rejection. MR nephro-urography/renography demonstrates structural data depicting urinary tract obstructions and functional data regarding the glomerular filtration and blood flow. MR angiography details the transplant vasculature and is particularly suitable for detecting vascular complications, with good correlation with digital subtraction angiography. Other functional MRI technologies, such as arterial spin labeling and MR spectroscopy, are showing additional promise. This review highlights MRI as a comprehensive modality to diagnose a variety of etiologies of graft dysfunction, including prerenal (e.g., renal vasculature), renal (intrinsic causes) and postrenal (e.g., obstruction of the collecting system) etiologies.

Key words: Magnetic resonance imaging; Diffusionweighted imaging; Diffusion-tensor imaging; Kidney transplantation; Dysfunction; Magnetic resonance renography; Blood oxygen level-dependent; Magnetic resonanc angiography; Functional evaluation



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Core tip: Kidney transplantation has been widely used clinically, and early detection of graft dysfunction with noninvasive imaging is crucial for postoperative management. Conventional imaging mainly focuses on morphology and has limited utility in functional aspects. Magnetic resonance imaging (MRI) has excellent soft-tissue contrast, and new technologies, such as diffusion-weighted imaging, diffusion-tensor imaging, blood oxygen level-dependent MRI, MR nephro-urography/renography, and MR angiography, provide more functional information and are therefore are well suited to graft evaluation. This review illustrates the utility of functional MRI as a comprehensive modality to diagnose a variety of etiologies of graft dysfunction.

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BACKGROUND

Renal transplantation has been established as the preferred treatment for patients with end-stage renal diseases. It provides better a quality of life by sparing patients from lifelong dialysis and reduces morbidity and mortality. Early characterization and monitoring of dysfunction after renal transplantation are crucial to allow effective treatments and to improve the chance of a successful outcome^[1]. Despite continuously improving surgical techniques and immunosuppressive therapies, surgical and medical complications can still arise. After renal transplantation, at least one episode of acute allograft dysfunction occurs in approximately 30%-40% of patients. These dysfunctions have a variety of causes, including prerenal (e.g., renal vasculature), renal (mostly intrinsic causes) and postrenal (e.g., obstruction of the transplant collecting system) etiologies^[2,3].

The assessment of such large range of pathologies is difficult and relies heavily on invasive biopsies, with a risk of graft injury and loss^[4]. Noninvasive imaging evaluation of transplanted kidneys has been widely used and offers anatomic evaluation of possible complications; however, medical complications, such as acute and chronic rejection, acute tubular necrosis (ATN), and drug-related toxicity, remain diagnostic challenges^[5]. The utility of magnetic resonance imaging (MRI) in transplanted kidneys has been described for both anatomic and functional aspects, and it offers critical insights into the above-mentioned problems^[6-8]. In addition to the conventional MR sequences, new technologies, such as diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI), blood oxygen level-dependent (BOLD) imaging, nephro-urography, renography, and MR angiography (MRA), are being tested, and increasing amounts of clinical data are available. This article reviews the research progress of these technologies on the functional assessment of renal allograft and describes their specific clinical applications to diagnose various causes of graft dysfunction.

DWI AND DTI

Initially developed for the diagnosis of acute stroke, DWI has recently gained increasing importance in imaging beyond the brain for functional assessment^[9]. Any clinical MR unit can provide diffusion-weighted images by adding two equally large but opposite magnetic field gradients. Improved MR systems allows better magnetic field homogeneity, more effective fat suppression, fewer distortion artifacts and, probably most importantly, much stronger imaging gradients, therefore generating high-quality images with a sufficient signal-to-noise ratio^[5]. Compared to brain imaging, DWI in the lower abdomen is challenging due to motion-related artifacts. Optimization includes the reduction of echo times and geometric distortions, and nearly all examinations are performed by using echo planar imaging (EPI) sequences in the kidneys^[10-12]. For quantitative image analysis, DWI yields a total "apparent diffusion coefficient" (ADCT) that provides information on diffusion and perfusion properties simultaneously if their contribution to total tissue diffusion can be separated. It is recommended that the ADCs of the medulla and cortex of the kidneys be analyzed separately if possible, due to their different intrinsic characteristics^[5].

In the kidneys, diffusion properties may be anisotropic because the main structures, such as vessels and tubules, exhibit a radial orientation, but DWI does not account for the directionality of molecular motion. The fractional anisotropy (F_A) of the kidneys can be assessed by DTI. The images can also be acquired with EPI sequence, and parametric ADC and F_A maps can be calculated online during image postprocessing^[13].

There currently are relatively limited data on the use of DWI in the assessment of transplanted kidnevs. Thoeny et al^[10] investigated the DW imaging of transplanted kidneys in fifteen patients in stable condition and native kidneys in fifteen matched healthy volunteers. They measured ADCT, an ADC reflecting pure diffusion (ADC_D) and the perfusion fraction (F_P). Compared with normal kidneys, renal allograft exhibited a lack of corticomedullary difference in the diffusion parameters. The authors claimed it was probably due either to the denervation of transplanted kidneys or to the secondary effects of immunosuppressive drugs. They also measured the within-subject parameters of repeated MRI, and coefficients of variation indicated that ADC was highly reproducible. In the same study, several examples were shown that focal hyperintense areas (corresponding to low ADC) might suggest acute rejection (AR) in pathological examinations.



Eisenberger *et al*^[14] presented similar results on the lack of corticomedullary difference of transplanted kidneys using DWI. Moreover, they compared renal allografts with stable function and those with AR or ATN soon after transplantation, using histology sections from the biopsies as the reference. The results showed that the ADC^T values and, more remarkably, F^P were reduced in transplanted kidneys with AR and ATN, while ADC_D stayed relatively similar for all subjects. F_P values strongly decreased to less than 12% in the cortex and medulla of renal transplants with AR and ATN. The estimated glomerular filtration rate (eGFR) was shown to be significantly correlated with the FP in the cortex and medulla, but not with ADCT or ADCD. Therefore, the authors proposed FP as the most accurate indicator for allograft function assessment soon after transplant.

More recently, Kaul *et al*^[15] compared DWI of renal allograft on the 7th day post-transplantation and corresponding kidney biopsy results. The ADC values were found to be slightly lower in the medulla compared with the cortex in transplanted kidneys with normal function. They also reported a significant reduction of ADC values in both the cortex and the medulla in allografts with abnormal function. More remarkably, such a reduction was correlated with the degree of rejection on the biopsies. Furthermore, the increase in ADC values was observed during the recovery from rejection, suggesting the usefulness of DWI for therapy monitoring after rejection episodes.

Lanzman et al^[13] conducted DTI in addition to DWI in patients with kidney transplants. They employed eGFR to differentiate allografts into good or moderate function and impaired function. In functionally impaired renal allografts, both FA and ADC of the renal medulla and cortex were significantly lower, and the corticomedullary difference in FA values was also lower. The FA of the medulla exhibited a high correlation with eGFR, while that of the cortex did not. In a more recent study conducted by Fan et al^[16], similar results were reported, and the FA of the medulla was proposed as a valuable indicator of allograft function. These data indicated that the results of DTI were generally concordant with DWI, while DTI might offer additional information on the differences between the renal medulla and cortex caused by anisotropy.

BOLD MRI

With the ability to measure intrarenal oxygenation, BOLD MRI has been used in native kidneys and has shown differences in medullary oxygenation during pathological conditions such as renal artery occlusion, water diuresis, and pharmacologic stimulation with Lasix, acetazolamide, and nitric oxide^[17,18]. Most published studies used a multiple gradient-recalled-echo sequence to perform BOLD MRI^[10,19,20]. This technique generates the parameter of R2*, which is a measure of the rate of signal loss in a specific region and is related to the concentration of deoxyhemoglobin. Usually, R2* levels are measured using the regions of interest (ROIs) tool. Experienced radiologists position certain numbers of ROIs in the cortical region and in the medullary region on the color R2* map.

Thoeny *et al*^[10] compared BOLD images of the kidneys in patients with renal allografts and in healthy volunteers. Medullary R2* was observed to be significantly lower in the patients than in the volunteers. Moreover, coefficients of variation of repeated MRI showed that R2* was quite reproducible. This study investigated the correlation of parameters of DW imaging and BOLD imaging. In transplanted kidneys, R2* correlated negatively with ADCT and ADCD in the medulla.

Sadowski et al^[19] also conducted BOLD MRI in patients who had received renal transplants. Twenty patients were included who had normal renal function, biopsy-proved ATN or AR. R2* values for the medulla were significantly lower in the AR group than the normal group and the ATN group. Using a certain threshold R2* value (18/s in this study), AR could be differentiated from normal function and ATN. R2* values for the cortex were higher in the ATN group than in the normal group and the AR group. More recently, Han et al[20] revealed similar results in a much larger patient group (110 patients). Sadowski et al^[19] reported that the decreased R2* values in the medulla of kidneys with rejection could be due to changed hemodynamics and/or to reduced local oxygen consumption caused by decreased tubular function. These results established BOLD MRI as a promising tool to differentiate between AR and ATN.

MR NEPHRO-UROGRAPHY/RENOGRAPHY

MR nephro-urography/renography assessment of the renal allograft combines structural and functional data within a single imaging examination. While T2W images provide excellent anatomic information, postcontrast T1W 3D gradient-echo images have the capacity to provide functional data in addition to tissue enhancement. New advances in the quick acquisition of dynamic, postcontrast, time-resolved images and delayed postcontrast excretion urographic images have introduced comprehensive MR nephro-urography and renography, enabling guantitative measurements of renal function, including individual kidney GFR and renal blood flow, in postprocessing. More recently, multicompartmental kinetic modeling was applied in the postprocessing of MR renography, generating separate parameters for the vascular and tubular compartments^[21-24]. This model benefits from the use of the lowest possible concentration of gadolinium-chelate^[3].

To assess intrinsic causes of renal dysfunction, such as AR and ATN, Yamamoto *et al*^[24] performed quantitative low-dose 3D MR renography on sixty patients with transplanted kidneys. The GFR and the mean transit time (MTT) of the tracer were calculated using a multicompartment renal model. GFR and MTT_K (MTT for the whole kidney) were significantly lower in the acute



Ref.	Year	No. of Pt	Contrast	Criteria for artery stenosis	MRA findings	Reference and accuracy
Huber et al ^[28]	2001	41	Unclear ^a	> 0% as clinically significant	23 significant artery stenosis, 2 vein complications, 4 perfusion defects of the parenchyma	DSA; Se: 100%; Sp: 93%-97%
Gufler <i>et al</i> ^[33]	2008	63	Gd-DTPA	< 50%: mild; 50%-70%:moderate; > 70%:severe	Artery stenosis: 29 mild, 3 moderate, and 1 severe	DSA for severe stenosis, one overestimati-on
Lanzman et al ^[34]	2009	20	None (SSFP)	$\geq 50\%$ as clinically significant	6 significant artery stenosis	DSA; Se: 100%; Sp: 88%
Liu et al ^[30]	2009	13	None (SSFP)	$\geq 50\%$ as clinically significant	1 significant artery stenosis	Stenosis confirmed by DSA
Ismaeel et al ^[31]	2011	30	Unclear ^a	\geq 50% as clinically significant	15 significant artery stenosis	DSA; Se: 93.7%; Sp: 80%
Bashir et al ^[32]	2013	16	Ferumoxytol	Unclear	2 moderate to severe stenosis, 1 occlusion	Stenosis and occlusion confirmed by DSA
Hwang et al ^[1]	2013	144	Gadobutrol	< 50%: mild; 50%-70%: moderate; > 70%: severe	Artery stenosis: 10 mild, 5 moderate, and 8 severe; 17 renal parenchymal infarctions	Severe stenosis confirmed by DSA
Tang et al ^[29]	2014	75	None (SLEEK)	$\geq 50\%$ as clinically significant	14 artery stenosis (10 significant), other complications such as arteriovenous fistulas and pseudoaneurysms	Significant stenosis: DSA positive predictive value: 91%

^aWith contrast, but unclear about the specific name. Pt: Patients; SSFP: Steady-state free precession; SLEEK: Spatial labeling with multiple inversion pulses; DSA: Digital subtraction angiography; Se: Sensitivity; Sp: Specificity; MRA: Magnetic resonance angiography.

dysfunction group than the normal function group. More specifically, the MTT_{A/K} (fractional MTT of the tracer for the vascular compartment) was significantly higher in the AR group than in the normal function group or the ATN group. The MTT_{T/K} (fractional MTT of the tracer for the tubular compartment) was significantly higher in the ATN group than in the normal function group or the AR group. The authors therefore claimed that this technique might help discriminate between AR and ATN. Researchers have also explored the use of other quantitative parameters, such as the medullary nephronal washout rate and the cortical arterial blood volume, but the results are still preliminary^[25].

To assess the postrenal etiology of renal allograft dysfunction, MR nephro-urography/renography offers functional information in addition to the exceptional soft-tissue contrast provided by standard MR images. Kalb *et al*^[3] has demonstrated how MR nephro-urography can guide clinical management the with abovementioned advantages. In addition to identifying anatomic variations, obstruction of transplant ureters, and fibrosis at certain anastomotic sites secondary to chronic ischemia, MR nephro-urography can enable precise measurement of GFR, thereby reflecting graft function.

MRA WITH OR WITHOUT CONTRAST

Vascular complications, such as artery stenosis, are relatively uncommon and are reported to occur in 5%-15% of transplanted kidneys, but they are a major cause of transplant loss, which usually necessitates resuming dialysis^[26,27]. Early and accurate diagnosis becomes critical because such complications are often correctable, and timely intervention can help salvage the graft kidney. Several studies have revealed the ability of

MRA to assess the renal parenchyma and peritransplant regions as well as vascular abnormalities^[1,28].

After conventional T1-weighted and T2-weighted sequences, an additional respiratory triggered 2D steady-state free precession (SSFP) sequence could be performed to visualize the vascular structure and generate reference images for planning the 3D contrastenhanced MRA. A 3D gradient-echo sequence could then be initiated for angiography if contrast is used^[1,29].

Table 1 displays the main findings of the studies investigating the use of MRA for the assessment of transplanted kidneys^[1,28-34]. The primary strength of MRA is evaluating the stenosis of relevant arteries, and the results of these studies have shown a generally good correlation of MRA with digital subtraction angiography (DSA), which is the golden standard for vascular abnormalities. Other vascular complications, such as vein stenosis and arteriovenous fistulas, can also be detected; several studies have also reported the use of MRA to detect renal parenchymal infarctions and perfusion defects^[28,30].

There has been an ongoing discussion about the use of contrast agents. Early results have shown that time-of-flight MRA had inferior diagnostic effectiveness compared to contrast-enhanced MRA^[28]. In addition to conventional gadolinium chelate-based contrast agents, new contrasts claiming to be nonnephrotoxic, such as ferumoxytol, have been used in clinical trials. The initial findings of Bashir *et al*^[33] in renal transplant MRA using ferumoxytol have demonstrated excellent depiction of the transplant vasculature.

Recently, unenhanced MRA with advanced techniques, such as SSFP alone and spatial labeling with multiple inversion pulses, has made substantial progress and has been reported to be of comparable image quality and diagnostic accuracy with contrast-enhanced $MRA^{[30,31]}$. However, the image quality of different artery segments might vary, as the image quality of the branches was observed to be inferior to that of the main arteries^[34].

OTHER FUNCTIONAL MRI TECHNIQUES

Arterial spin labeling (ASL) MRI was developed to measure tissue perfusion data and has been used extensively in the brain. Lanzman *et al*^[35] conducted ASL MRI in 20 renal allograft recipients, divided into a good function group and an acute deterioration of renal function group. Quantitative measurement showed that cortical perfusion values were significantly reduced in transplanted kidneys with impaired function^[35]. Another study evaluated the reproducibility of ASL MRI in both native and transplanted kidneys. Intraclass correlation and coefficients of variation indicated that this technique was reproducible in the cortexes of native and transplanted kidneys, but that it demonstrated moderate to poor reproducibility for intravisit and intervisit measures in the medulla^[36].

Studies have reported that chronic allograft dysfunction is accompanied by a decrease in the β -ATP/Pi ratio, a marker of kidney high-energy phosphate metabolism, as assessed by ³¹P- magnetic resonance spectroscopy (MRS), and that a relatively high β -ATP/Pi ratio (> 1.20 AU in one study) might indicate a good graft survival (probability > 3 years). Early improvement in the β -ATP/Pi ratio (within 6 mo) in renal transplant patients receiving short-term low-dose valsartan treatment can be detected by ³¹P-MRS^[37].

Magnetic resonance elastography (MRE) generates a quantitative measurement of tissue stiffness and has been widely used in the liver to assess the degree of fibrosis. Lee *et al*^[38] performed MRE on 11 renal transplant patients and compared calculated the tissue stiffness value with histologic results. The mean stiffness value of patients with moderate interstitial fibrosis was higher than that of patients with mild or no interstitial fibrosis, but not significantly so. The authors suggested that multiple factors can influence renal stiffness^[38].

COMPARISON OF OTHER MODALITIES AND CLINICAL INDICATIONS

In evaluating transplanted kidneys, several imaging modalities are available for clinicians. The dysfunction of renal grafts is often clinically asymptomatic and presents only with an isolated increase in serum creatinine. To detect intrinsic etiologies, such as ATN or AR, color Doppler ultrasonography (US) is widely used because of its convenience and lack of radiation or toxic dye. However, it is user-dependent and its findings are often nonspecific for a final diagnosis or confirmation of normal function. Nuclear medicine (NM) imaging can be used to establish the flow, but its results can also be nonspecific to identify etiologies of dysfunction, Wang YT et al. Functional MRI of transplanted kidneys

and it is time-consuming and not readily available^[8]. Functional MR technologies, such as DWI and DTI, could be recommend when patients have clinically suspicious intrinsic etiologies of graft dysfunction and negative or obscure results from US or NM imaging. Furthermore, these technologies have potential to monitor graft function during therapies. Quantitative measurements by BOLD MRI or 3D MR renography (especially when a multicompartment renal model is available) are worth considering to further differentiate between AR and ATN.

US is usually considered the first-line test to assess urologic obstructions, but the relatively poor anatomic detail it allows could lead to failure to identify the causes of the obstruction^[3,8]. Computed tomography (CT) can be used to detect nephrolithiasis-related obstructions, but it uses iodinated radiation and carries the risk of contrast nephropathy. MR nephro-urography can be recommended in such cases. With the exceptional soft-tissue contrast, MR nephro-urography may reveal causes such as anatomic variations and fibrosis at certain anastomotic sites while generating the precise value of GFR at the same time.

To evaluate vascular complications, US is generally used first, but it may be limited by the interposition of bowel gas between the transducer and the graft, and by issues of angulation and tortuosity caused by the irregular curvilinear anatomy of transplanted renal arteries. In addition, US cannot accurately visualize allograft artery stenosis in patients with high peak systolic velocities at the anastomosis^[1,8]. DSA is confirmatory and has the capacity of simultaneous interventions, but it is invasive and expensive. Computed tomographic angiography is valuable for evaluating graft vessels, but again, it uses iodinated contrast agents and exposes the patient to ionizing radiation. Gadolinium chelate-based contrast agents used in enhanced MRI are believed to be generally safer, and MRA without contrast with improved image guality and diagnostic accuracy has been proposed^[30,31,34]. Abundant evidence has shown the good correlation of MRA with DSA. Usually, patients with suspicion of transplantrelated renal vascular complications, such as refractory hypertension and/or worsening graft function, elevated serum creatinine levels and nondiagnostic US findings are examined with MRA, which can assess renal parenchyma blood supply and the peritransplant region conditions in addition to the vascular abnormality.

MRI has limitations in clinical practices as well. It is less frequently available because, unlike US, the equipment is not portable, the cost is relatively high, and it requires specialized personnel who may not be available 24 h/d. Moreover, it carries the risk of nephrogenic systemic fibrosis in patients with a GFR lower than 30 mL/min per 1.73 m² in gadolinium-based studies^[8]. As with all medical procedures, a rational judgment must be applied to weigh the potential benefits against the risks.

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CONCLUSION

To summarize, renal transplantation has been widely used clinically, and MRI is a noninvasive technique well suited for the assessment of renal allografts. Given the functional information provided by new technologies, MRI should be considered as a promising and powerful tool in the diagnostic workup for a variety of renal pathologic conditions, and it has the potential to significantly influence the postoperative management of kidney transplant patients. To further improve its diagnostic accuracy, a more comprehensive understanding of MRI, as well as knowledge of clinical situations, is recommended. The use of reproducible and representative quantitative parameters could be further explored, and clinical trials with larger sample sizes and solid references could offer critical clues.

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