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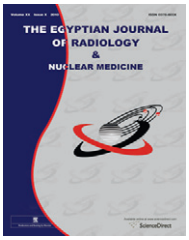

ORIGINAL ARTICLE

Computer aided detection of acute renal allograft dysfunction using dynamic contrast enhanced MRI

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KEYWORDS

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Computerized

Abstract *Aim of the work:* To evaluate the feasibility of dynamic contrast enhanced (DCE) MR Renography (MRR) in evaluation of renal allograft dysfunction using the computer based technique for motion correction and creation of renographic curves.
Materials and methods: Between April 2007 and March 2008, 55 consecutive patients underwent kidney transplantation at our center from live related donors. There were 42 men and 13 women. The patients were divided into two main groups; first group (23 patients) included patients with stable graft function as indicated by normal serum creatinine ($\leqslant$1.3 mg/dl). The second group (32 patients) included patients with acute kidney dysfunction as indicated by elevated serum creatinine. All were examined by DCE-MRI, ultrasound-guided needle biopsy was done for all the patients in the second group after MRI study.
Results: There were 23 patients with normal graft function (group 1) and 32 patients with acute graft impairment (group 2); 24 with acute cellular rejection and eight with acute tubular necrosis (ATN). Morphological evaluation revealed preserved corticomedullary differentiation (CMD) in

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group 1 while in group 2 there were poor CMD in 16 cases and lost CMD in nine cases. Functional evaluation using the mean intensity of the medullary region, to create MR Renographic curves, was used with sensitivity, specificity and accuracy of 75%, 96% and 84%, respectively.

Conclusion: Computer aided analysis of renographic MR curves and the mean intensity of the medulla region have more important features than maximum intensity, it allows separation of normal kidney from impaired one but it cannot differentiate the underlying causes of the graft dysfunction.

1. Introduction

Acute rejection – the immunological response of the human immune system to the foreign kidney – is the most important cause of graft failure after renal transplantation (1).

Imaging of transplanted represents a challenge, as the diagnosis of graft dysfunction depends mainly upon the needle biopsy which is an invasive technique and carries the risk of many complications.

In the last two decades new imaging modalities of functional assessment of transplanted kidney by ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) by generation of time intensity curves allowed both anatomical and physiological evaluation of the kidney in the same time (2).

Many diagnostic attempts have been made to reduce the need for an invasive transplant biopsy, considered the "gold standard" for the diagnosis of parenchyma dysfunction. In a study done by Benozzi et al., they confirmed that contrast enhanced US (CEUS) using microbubbles is a noninvasive, easy technique, which provides information on renal tissue microcirculation and regional parenchyma flow. It identified the early graft dysfunction (3). In another study done by Eisenberger et al., they found that diffusion weighted (DW)-MRI allows reliable determination of diffusion and microcirculation contributions in renal allograft shortly after transplantation; deviations in acute rejection indicate potential clinical utility of this method to non-invasively monitor derangements in renal allograft (4).

The most consistent sign of acute rejection reported is the loss of corticomedullary differentiation on contrast enhanced MR Renography (5). In DCE-MRI, a contrast agent called Gd-DTPA is injected into the bloodstream, and as it perfuses into the organ, the kidneys are imaged rapidly and repeatedly. During the perfusion, Gd-DTPA causes a change in the relaxation times of the tissue and creates a contrast change in the images (6). Image intensity curves generated from dynamic MRI may provide functional information of the kidney. Patients with acute rejection have significantly decreased cortical and medullary perfusion (7). The limitations of functional contrast enhanced MRI include quantification of gadolinium concentration from signal intensity, image postprocessing problems such as spatial registration of the dynamic data and tissue segmentation (8).

In this study we evaluate the feasibility of DCE MR Renography (MRR) in characterization of the enhancement patterns of different renal compartments (medulla versus cortex) in kidney transplant recipients, with normal versus impaired renal function, using the computer based technique for motion correction and creation of renographic curves.

2. Material and methods

Our institutional review board approved the study protocol, and consent was taken from all our patients. The study included 55 consecutive patients underwent kidney transplantation at our center from live related donors. There were 42 men and 13 women, their mean age was 29.4 ± 10.2 years (range 10–52). We divided our patients into two main groups; first group (23 patients) included patients with the kidney function within normal range as indicated by normal serum creatinine (below or equal 1.3 mg/dl) and all cases had glomerular filtration rate (GFR) above 30 ml/min. The second group (32 patients) included patients with acute kidney dysfunction as indicated by elevated serum creatinine. Ultrasound study of the transplanted kidneys was done for all cases as a routine investigation including gray scale and power Doppler sonography to exclude urinary obstruction or perirenal collections and to assess vascular patency. Ultrasound-guided needle biopsy was done for all the patients in the second group after MRI study. All were examined by DCE-MRI 14 days after transplantation as a basal study for the first group and the second group was examined at variable post-transplantation intervals (mean 26, range 1–47 months).

2.1. MR Imaging protocol

MRI study was performed with a 1.5T imager (Signa-Horizon, GE medical system, Milwaukee, WI, USA). We started dynamic MRI (dMRI) by a coronal fast-spoiled gradient (FSPGR) T1-w image with fat suppression at the center of the kidney before injection of gadolinium with the following parameters (5 mm thickness, interslice gap = 1 mm, TR = 30–40 ms, TE = 2–3 ms, Flip angle 70°, FOV 38 × 38 cm and the matrix 256 × 160). Then, furosemide (0.1 mg/kg) was injected intravenously through antecubital vein followed immediately by 0.1 mmol/kg gadoteric acid (Dotarem 0.5 mmol/ml; Guerbet, France) at 3 ml/s and the coronal scan series was repeated every 30 s for 5 min, then six coronal images were taken 10 min later. Finally, the total number of obtained images was 72.

2.2. Analysis of MRR

We performed morphological analysis of all the dynamic MRI images to detect the renal size, contour, cortex, medulla and calyceal system to detect areas of hyper- or hypovascularity of parenchyma or dilatation of the collecting system.

Functional analysis was done in collaboration with the Department of Computer Vision and Image Processing (CVIP) Lab., Electrical and Computer Engineering Department, University of Louisville, USA. The level set function proposed by Farag and Hassan was used (9). We obtained 72 slices for each

kidney sequence of DCE-MRI. The medulla region could not be distinguished from the cortex region approximately after first 25 slices in DCE-MRI because of low contrast difference as shown in Fig. 1. To solve this problem, one slice of each dataset on which the renal cortex was clearly distinguishable from the medulla was segmented into its cortex and medulla regions using the level sets method. Hence, each kidney subject had its own cortex and medulla masks which were used to segment the other 71 slices. These masks were propagated to all slices.

After the segmentation was completed, motion correction was done using non-rigid registration then the renograms of each data set were obtained based on the mean and maximum gray level value of the cortex and medulla regions. The mean of these vectors was obtained to be used as a normal and rejected reference. These renograms are shown in Figs. 2–5.

In Figs. 2 and 3, the *y*-axis shows the mean and the maximum intensity of the medulla region, respectively. In Figs. 4 and 5, the *y*-axis shows the mean and the maximum intensity of the cortex region, respectively. In all figures, *x*-axis shows slice number (frame/scan).

We considered the washout of contrast when there was continuous decay of signal intensity (SI) after the contrast peak, which we considered normal, persistence of high SI after the first peak, or continuous rise of the curve, was considered abnormal.

We used the histological results of the needle biopsy as gold standard for the kidney dysfunction.

All patients had a GFR above 30 ml/min and none of the patients was on dialysis.

3. Results

The final analysis included 23 patients with normal graft function (group 1) and 32 patients with acute graft impairment (group 2). In the second group the final histopathological diagnosis was acute cellular rejection in 24, and acute tubular necrosis (ATN) in eight patients. No one of our patients had contraindication to MR study and no one developed nephrogenic systemic fibrosis with follow-up duration > 6 months.

3.1. Morphologic evaluation

All the kidneys of both groups were of regular contour and normal dimensions; the range of long axis was 10.5–12 cm for both groups. The corticomedullary differentiation (CMD) was good at MRI in all patients of the first group while in the second group the CMD was good in seven cases (22%), poor in 16 cases (50%) and lost in the remaining nine cases (28%). Perfusion defects were not detected in any of these cases with normal vasculature at both MRI and Doppler US. No hydronephrotic changes at all kidneys with preserved excretory function.

3.2. Functional evaluation

At computer analysis of renographic curves after applying two regions of interest, one for the cortex and one for the entire medulla. The cortex regions did not provide enough information to distinguish rejected and normal kidneys. Figs. 4 and 5 showed the response of the cortex regions for both rejected and normal kidneys. Based on perfusion analysis of the renal cortex the distinction between normal and decreased renal function was 50%.

Analysis of computer generated curves for the medulla showed short time to peak enhancement and early washout of contrast in the normal kidneys. While in acutely impaired function of the graft, the DCE-MRI images showed a delayed perfusion pattern and a reduced enhancement with prolonged time to peak and delayed washout of contrast. There was overlap between the SI of the patients with acute rejection and acute tubular necrosis. These two entities could not be separated on the basis of renographic curves analysis.

The results of using the medullary region are based on the mean intensity of the whole medulla versus the maximum intensity as described in Table 1 showed that the overall accuracy, sensitivity and specificity of the mean intensity was 84%, 75% and 96% versus 55%, 50% and 65%.

When we used the mean signal intensity of the renal medulla there were eight cases with false negative and one case with false positive diagnosis while with the maximum intensity of

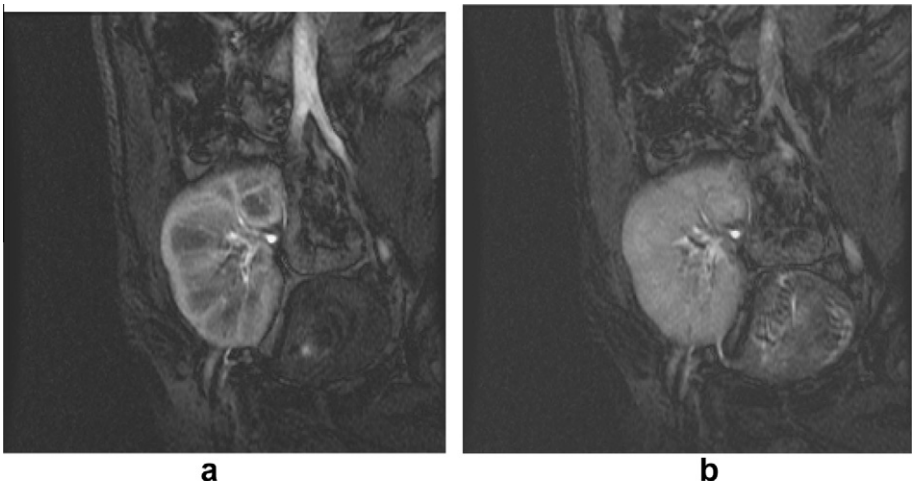

Figure 1 Two sample slices of same clinical data set of a 35 years old male with the kidney function within the normal range, (a) the cortex and medulla regions can be easily distinguished in the 6th slice, (b) the cortex and medulla region cannot be distinguished in the delayed 60th slice because of low contrast between two regions.

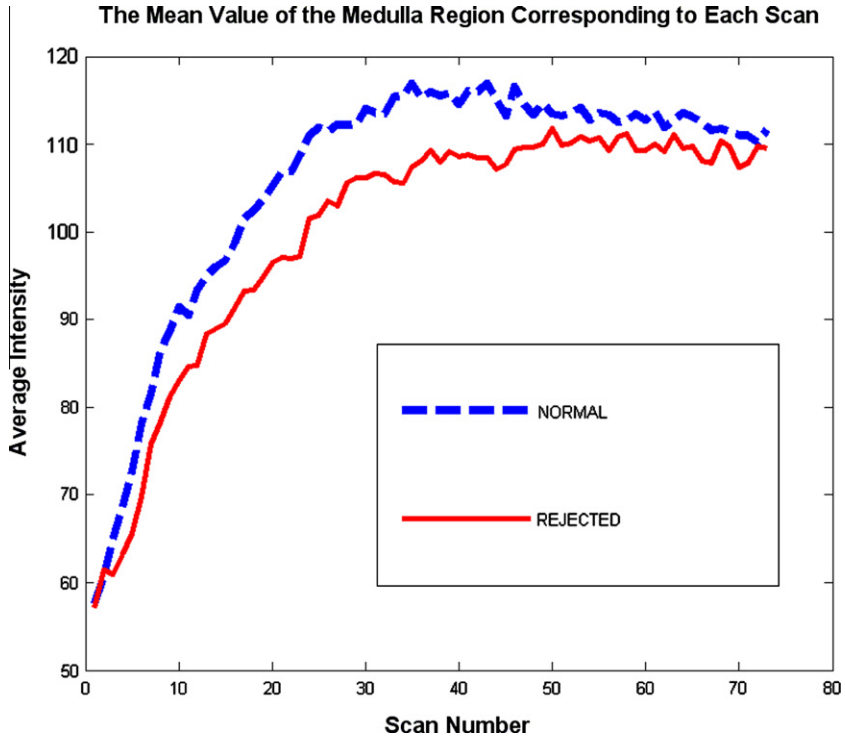

Figure 2 The time intensity curve of normal and rejected kidneys based on the mean (average) intensity values of the medullary region.

the medulla there were 16 cases with false negative and seven cases with false positive diagnosis.

4. Discussion

Acute graft impairment is a diagnostic challenge. It can occur at any time after transplantation. The cause can sometimes be suspected on clinical basis. An ultrasound examination that includes a Doppler flow study can demonstrate renal allograft enlargement, the presence or absence of hydronephrosis, and blood flow in and out of the kidney graft (10).

Early detection of the kidney rejection is important for the treatment of renal diseases. Although renal biopsy with histopathology assessment is the gold standard for diagnosing acute

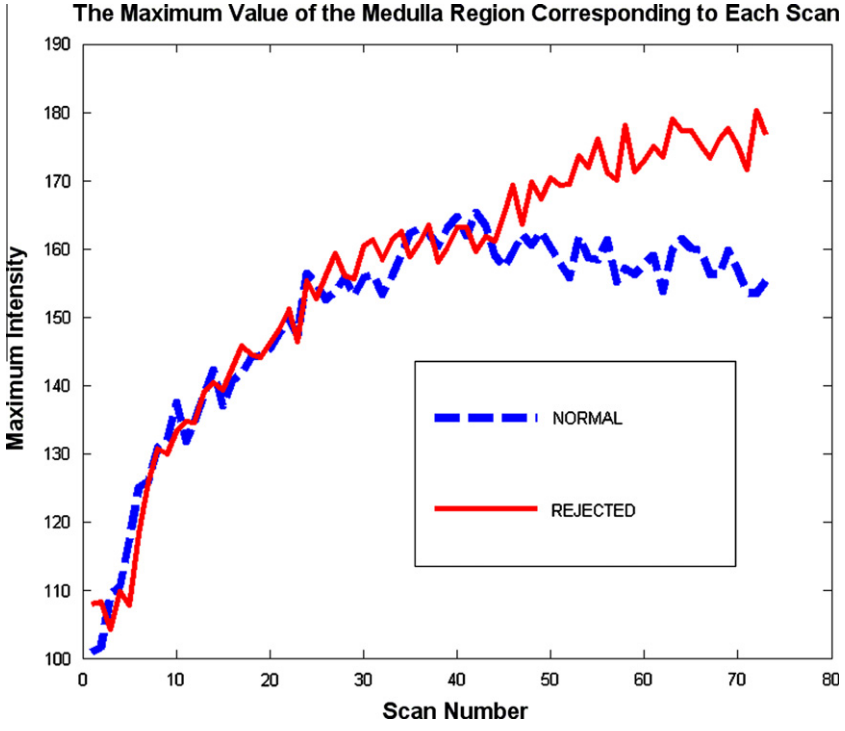

Figure 3 The time intensity curve of normal and rejected kidneys based on the maximum intensity values of the medullary region.

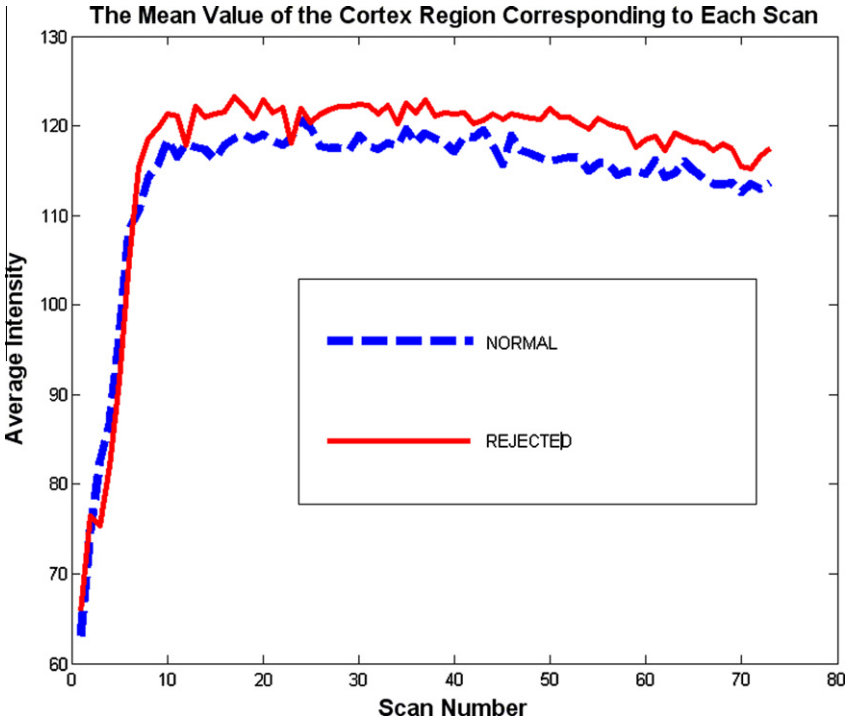

Figure 4 The time intensity curve of normal and rejected kidneys based on the mean (average) intensity values of the cortex region.

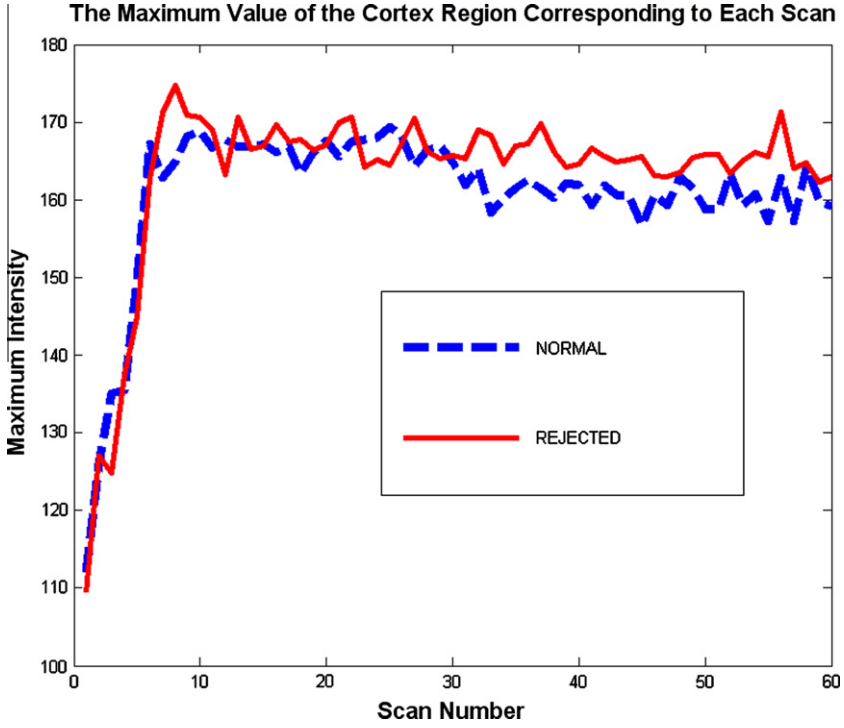

Figure 5 The time intensity curve of normal and rejected kidneys based on the maximum intensity values of the cortex region.

graft rejection, it is an invasive procedure and is liable for serious complications (11). Hence, researchers have been trying to find a diagnostic method with less complications.

In a study done by Kikinis et al. (12) on healthy volunteers, they observed SI drop in the medulla at around 105 s and SI loss in renal pelvis later in the examination. Using various techniques, Rohrschneider et al. (13), Teh et al. (14) and Grattan-Smith et al. (15) have demonstrated agreement between dynamic diuretic MR and isotopic renography, the reference examination. Moreover, some authors (13,14,16) suggested

Table 1 The total accuracy, diagnostic specificity, and diagnostic sensitivity for the medulla.

Method	Mean intensity	Maximum intensity
Total number of subjects identified correctly	46	30
Total number of subjects tested	55	55
Total accuracy (%)	84	55
Number of normal subjects identified correctly	22	15
Number of normal subjects tested	23	23
Diagnostic specificity (%)	96	65
Number of rejected subjects identified correctly	24	16
Number of rejected subjects tested	32	32
Diagnostic sensitivity (%)	75	50

that MRR could compete with isotope renography. Dynamic analysis can be used in evaluation of kidney function by the contrast transit at the cortex and medulla.

In a study done by Katzberg et al. (17), it was emphasized that the MRI was the only modality that accomplished the anatomic, dynamic and functional information of the normal and abnormal kidneys. They stated that nuclear medicine renography provides functional information, but relatively of poor spatial resolution, US has better spatial resolution than nuclear medicine but provides no functional information while CT provides excellent spatial resolution and the potential to assess renal dynamics, but multiple exposures would be needed, resulting in high dose radiation.

In a similar study done by Nakashima et al. (18), coronal turbo FLASH dynamic images were obtained every 5 s for 5 min after an intravenous bolus injection of Gd-DTPA. CMD on spin echo coronal T_1-weighted images and MR renogram patterns of the renal cortex and medulla were obtained and they found that in patients with severe renal dysfunction, the arterial cortical peak was indistinct.

We introduced a new computer aided approach to classify normal kidney function from kidney rejection using dynamic contrast enhanced magnetic resonance imaging. The data sets used in our experiments were acquired prior to biopsy. We realized that the medulla region has specific responses to DCE-MRI that were helpful identifying kidney rejection. Our result shows that the response of medulla regions to DCE-MRI may be helpful distinguishing kidneys with impaired function from normal kidneys. There was an overlap between SI of the cases with ATN and acute rejection and further extended workup is recommended to differentiate between the underlying causes of renal dysfunction.

For MMR, there are some limitations including the general limitations for MRI such as claustrophobia, metallic prostheses and pacemakers. Also patients with renal impairment and GFR < 30 ml/min were excluded.

5. Conclusion

MR Renography is a clinically feasible technique that provides information about the renal function by studying changes of signal intensities within the renal parenchyma. In our study we conclude that the mean intensity of the medulla region has more significant features than maximum intensity in the assessment of renal dysfunction; it allows distinction of normal kidney function from impaired one, but we could not identify differences by the etiology of renal dysfunction. These preliminary results deserve further investigation in order to assess the potential of dynamic MR Renography to distinguish between etiologies of renal dysfunction without the side effects of biopsy.

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