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Diffusion-MR in kidney transplant recipients: is diuretic stimulation a useful diagnostic tool for improving differentiation between functioning and non-functioning kidneys?

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ABSTRACT

Objectives: To evaluate the effects of diuretic stimulation on Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI) techniques in transplanted kidneys.

Methods: 33 transplanted kidney recipients underwent DWI and DTI sequences before and after furosemide. Cortical and medullary Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) values were calculated in transplanted kidneys. Patients were divided into two groups according to their estimated glomerular rate filtration (Group A ≥ 60 ml/min and Group B < 60 ml/min). Wilcoxon matched pairs signed rank test was applied to compare pre- and post-furosemide values. ADC and FA values were compared between the 2 groups using a Mann-Whitney *U* test. Receiver Operating Curves (ROC) analysis was performed to predict normal renal function.

Results: Wilcoxon test revealed a statistically significant difference for all pre- and post- ADC and FA values in group B. For group A, a significant difference was found comparing pre- and post-medullary ADC and FA values ($p = 0.0151$ and $p = 0.0054$).

In the comparison between group A and group B, cortical and medullary mean ADC values were significantly different before and after furosemide. With regard to medullary FA values, a significant difference was found between groups before and after diuretic stimulation (p respectively of 0.004 and 0.042). Comparing cortical FA mean values, no statistical difference was observed between groups before and after furosemide.

The highest Area Under Curve values were reported for cortical ADC (0.878) and medullary ADC (0.863) before diuretic bolus.

Conclusions: In transplanted kidneys, furosemide did not improve the differentiation between normal and reduced function.

1. Introduction

Kidney transplantation is the treatment of choice for many renal diseases that lead to chronic failure. To improve long-term allograft survival, a careful monitoring of renal function is recommended. Currently, this evaluation may be carried out using invasive and non-invasive techniques [1,2]. Renal biopsy is an invasive and painful procedure, with risk of complications [3]. A non-invasive assessment represents the true diagnostic challenge.

In the past, renal evaluation in kidney transplant recipients was based mainly on creatinine serum levels and ultrasound examination, but these procedures had low sensitivity and showed renal damage when it is in an advanced stage [4]. In recent decades, Magnetic Resonance (MR) with Diffusion Weighted Imaging (DWI) [5–7] has been

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widely used for the assessment of renal function in many chronic kidney diseases. DWI measures the Brownian motion of water molecules and capillary perfusion in the extracellular extravascular space by calculating the Apparent Diffusion Coefficient (ADC) [8]. However, ADC is a quantitative parameter, which provides a measurement of global diffusion, but it cannot describe the directionality of molecular motion. In kidneys, as in brain white matter, molecular diffusion has a preferred orientation because tubules, collecting ducts and vessels are radially oriented toward the renal pelvis especially in the medulla, while the cortex contains randomly oriented structures. Because of this anisotropic structure, in addition to the ADC value, diffusion might be evaluated using diffusion tensor imaging (DTI) with at least six diffusion-sensitizing directions [9,10].

Fractional Anisotropy (FA) is derived from DTI sequences, and it expresses the preferred direction of diffusion due to the grade of anisotropy. It is calculated separately for cortex and medulla; as widely reported in literature, the FA value is higher in the medullary portion of the kidney [11,12].

DWI and DTI were able to differentiate normal from abnormal kidneys: many authors have emphasized the role of these techniques in the assessment of renal function in kidney transplant recipients [13–15]. They showed that ADC and FA values are generally lower in transplanted patients than in healthy volunteers, and also decrease with renal function decline [16]. A positive correlation was also found between estimated glomerular filtration rate and ADC values, and between estimated glomerular filtration rate and medullary FA value [4,16,17]. However, in differentiating normal and impaired renal function in a population of kidney transplant recipients, DWI and DTI may be limited by a certain degree of overlap among functional values.

To increase validation of these functional imaging modalities, many studies have investigated clinical conditions and functional parameters that could influence renal function [18–20]. Sigmund et al. showed how diffusion MR metrics are sensitive to flow changes induced by diuretic administration that inhibits water reabsorption and increases intratubular flow with tubular dilation [19].

Therefore, the aim of this paper is to assess the role of diuretic stimulation in differentiating normal and impaired renal function in a population of transplanted kidneys. In particular, this study analyzed ADC and FA values obtained before and after furosemide administration, in order to evaluate whether renal stimulation may reduce overlap among functioning and non-functioning kidneys, and if diuretic administration could be adopted – in a future clinical scenario – as an additional tool to diffusion MR in monitoring renal function.

2. Materials and methods

2.1. Population study

This single-center prospective study was performed from July 2015 to May 2017. The study was approved by our internal institutional committee and performed according to the principles of the Helsinki Declaration.

A total of 33 renal recipients were studied, comprising 20 males and 13 females, ranged between 28 and 78 years of age (mean age of 52.54 ± 12.16). All MR examinations were performed using a 1.5 Tesla MR scanner (Signa HDx MR System GE - General Electric).

Each renal transplant recipient underwent MR examination before and after furosemide administration.

Patient enrollment was performed following these inclusion criteria:

1. Creatinine Clearance (ClCr) values collected no > 24-48 h before MR examination;
2. Stable renal function, which means subjects having ClCr values collected within 1–6 months before MR, with no > 10 ml/min difference between samples.

On the basis of ClCr values, we divided patients into 2 groups: ***Group A*** – which included 15 subjects with normal renal function – having a ClCr ≥ 60 ml/min; ***Group B*** – which included 18 patients with impaired renal function – showing ClCr values < 60 ml/min.

MR contraindications and/or low quality of examinations acquired were adopted as exclusion criteria. All patients had provided written consensus prior to the MR examination.

The same surgical team performed the kidney transplantations. Transplanted kidneys were positioned in right iliac fossa in all patients – except for one recipient where an ipsilateral dual-kidney transplanted technique was performed.

Polycystic kidney disease and IgA nephropathy represented the most common reasons for kidney transplantation (16 and 11 cases respectively). Other indications for renal transplantation were: calcineurin nephrotoxicity (n = 1), unknown glomerulonephritis (n = 2), hypertensive glomerulonephritis (n = 1), membranoproliferative glomerulonephritis (n = 1) and Nail Patella syndrome (n = 1).

Among enrolled patients, there were two with renal rejections. The average period between transplantation and examination date in our population study was 4 years and eleven months.

Immunosuppressive therapy and comorbidities of kidney transplants recipients were annotated: tacrolimus and mycophenolate mofetil was the most common drug combination found (20 cases), followed by sirolimus and mycophenolate mofetil (n = 4); other combinations, less frequently encountered were everolimus and mycophenolate mofetil (n = 2), tacrolimus and everolimus (n = 2), sandimmun and mycophenolate mofetil (n = 2), sandimmun and everolimus (n = 1). Cortisone was administered to all patients.

Cardiovascular diseases (arterial hypertension and atrial fibrillation), diabetes mellitus and thyroid disorders were the most common comorbidities found in the group.

2.1.1. MR protocol

All patients observed no hydration or specific diet restrictions prior to MR examinations; in all cases, an antecubital vein access was provided for the furosemide injection.

The examinations were acquired using an 8-channel phased array coil.

The following sequences were included in our study protocol:

3. Triplane Localizer;
4. Coronal T2-weighted Fast Recovery Fast Spin Echo (FRFSE), acquired with the following technical parameters: TR 3260–4300 ms, TE 101–105 ms, FOV 30–36 cm, Matrix 256 × 256, NEX = 2–4;
5. Axial T2-weighted FRFSE, with TR = 2500–3800 ms, TE = 104–109 ms, FOV 38–48 cm, Matrix = 320 × 224, NEX = 2–4;
6. Axial fat suppressed T2-weighted FRFSE, with TR = 2880–4400 ms, TE = 81.2–82.7 ms, FOV = 38–48 cm, Matrix 320 × 224, NEX = 2–4;
7. Axial T1 FSE, with TR = 360–500 ms, TE = 7.5–8.3 ms, FOV = 38–48 cm, Matrix 320 × 192, NEX = 2–3;

DWI was acquired using free breathing single shot echo planar (SS-EP sequence) technique, with diffusion gradient active for any directions of the plane. Acquisition parameters were as follows:

- Axial DWI using b values of 0–500, with TR = 3000 ms, TE 95.8 ms, FOV 40 × 40 mm, Matrix = 160 × 160, NEX = 4;
- Axial DWI using b values of 0–800, with TR 3000 ms, TE 95.8 ms, FOV = 40 × 40 mm, Matrix = 160 × 160, NEX = 4;
- Axial DTI with 15 directions, TR = 7500 ms, TE = 82.7 ms, FOV = 40 × 36 mm, Matrix = 128 × 128, NEX = 4.

Functional sequences were repeated in the same orientation after intravenous administration of furosemide (20 mg/2 ml).

MR analysis was performed by 2 radiologists (***Reader 1*** and ***Reader 2*** – respectively with 15 and 3 years experience in abdominal MR): the