Clinical Imaging 53 (2019) 97–104

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Body Imaging

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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ARTICLE INFO

Keywords:
Diffusion tensor imaging
Diffusion magnetic resonance imaging
Furosemide
Kidney transplantation
Magnetic resonance imaging

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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https://doi.org/10.1016/j.clinimag.2018.10.003
Received 18 January 2018; Received in revised form 27 August 2018; Accepted 1 October 2018

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

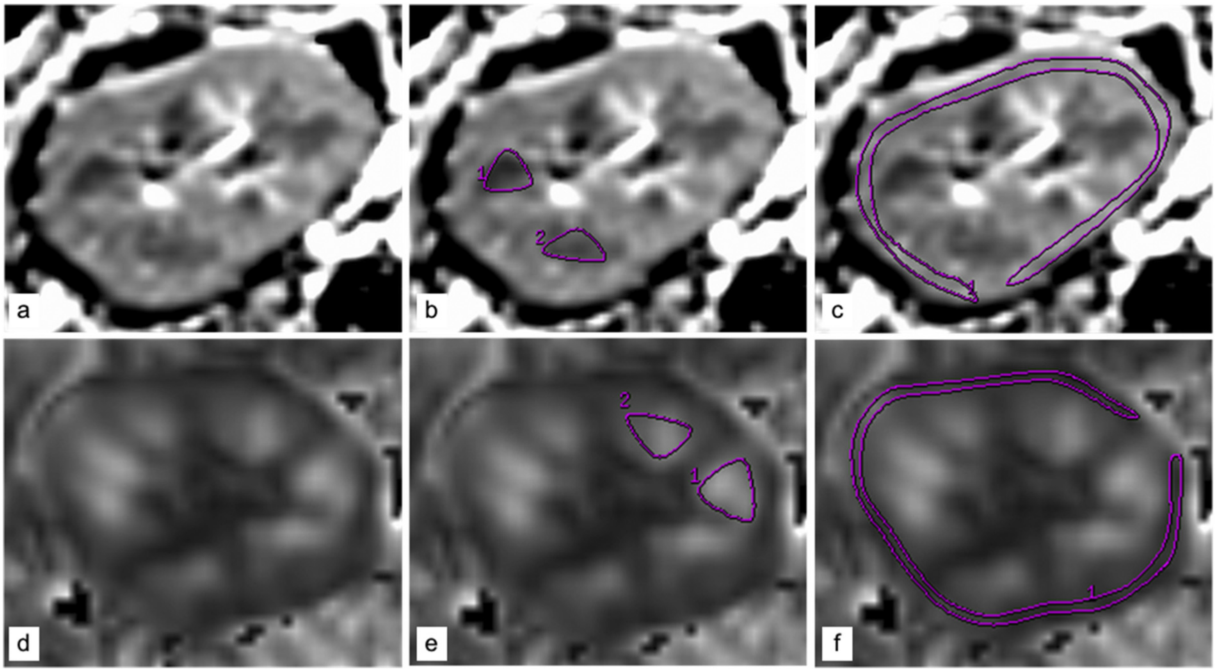

Fig. 1. Regions of Interests (ROIs) positioned on cortical and medullar regions for Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) assessment; medullary ADC and FA values were calculated tracing triangular-shaped ROIs centered on renal pyramids (Fig. 1b and e). Cortical measurements were obtained placing large sickle-shaped ROIs along the renal border (Fig. 1c and f).

Table 1
Inter-rater agreement (kappa coefficient) for c-ADC, m-ADC, c-FA and m-FA measurements among readers.

	c-ADCpre	c-ADCpost	m-ADCpre	m-ADCpost
k-agreement	0.903	0.746	0.872	0.802
CI	0.861–0.945	0.575–0.917	0.813–0.931	0.685–0.918

	c-FApre	c-FApost	m-FApre	m-FApost
k-agreement	0.792	0.850	0.797	0.797
CI	0.696–0.888	0.789–0.910	0.687–0.907	0.687–0.907

CI = Confidence interval.

examinations were independently evaluated, with readers blinded to their reports. Functional analysis was performed using a dedicated workstation (Advantage Workstation 4.6 General Electric) for DWI and DTI sequences post-processing.

ADC and FA values were assessed for each transplanted kidney by placing ROIs both on cortical and medullary regions (Fig. 1).

Cortical ADC (c-ADC) and cortical FA (c-FA) measurements were obtained placing a large sickle-shaped Region of Interests (ROIs) along the renal border into the upper, middle and lower portions of kidneys. Medullary ADC (m-ADC) and medullary FA (m-FA) values were achieved placing triangular-shaped ROIs centered on renal pyramids; for each kidney, two ROIs were drawn into the upper, middle and lower renal poles.

Finally, the average of the three ROIs drawn in cortical for c-ADC and c-FA mean values was obtained; similarly, m-ADC and m-FA mean values were achieved averaging all the ROIs positioned.

Morphological sequences were used as references to ROIs positioning avoiding vessels and kidney chalices. Measurements were performed on DWI and DTI sequences acquired before and after furosemide administration with ROIs placed in the same regions.

2.2. Statistical analysis

Statistical analysis was performed using MedCalc program (MedCalc version 11.4.4.0, MedCalc.

Software bvba©, Mariakerke, Belgium) and the Winstat statistic software.

Variations among readers were assessed calculating the inter-rater agreement (kappa coefficient). The strength of agreement was stated in the following categories: < 0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 very good.

Pre- and post-furosemide ADC and FA values were compared using Wilcoxon matched pairs signed rank test. Comparisons between c-ADC, c-FA, m-ADC and m-FA values of the two groups – before and after furosemide administration – were performed using the *U* test of Mann-Whitney with Holm-Bonferroni sequential correction.

Receiver Operating Characteristic (ROC) analysis was finally calculated to predict normal renal function (Group A).

3. Results

3.1. Inter-rater agreement

Table 1 shows the agreement reported between the 2 readers for ADC and FA values before and after diuretic stimulation. A very good agreement among readers was observed before furosemide for c-ADC (k = 0.903 CI = 0.861–0.945) and m-ADC (k = 0.872 CI = 0.813–0.931). Again, before stimulation the k-agreement was good for c-FA (k = 0.792 CI = 0.696–0.888) and for m-FA (k = 0.777, CI = 0.674–0.879). After diuretic stimulation, a good agreement was also reported for c-ADC (k = 0.746 CI = 0.575–0.917) and m-FA (k = 0.797 CI = 0.687–0.907); a very good agreement was reported for c-FA and m-ADC – with k = 0.850 (CI = 0.789–0.910) and k = 0.802 (CI = 0.685–0.918) respectively.

3.2. Pre- and post-furosemide Wilcoxon analysis

Median values of cADC, mADC, cFA, and mFA obtained before and

Table 2
Pre- and post-diuretic stimulation median values of cortical and medullary ADC and FA; delta values and associated *p*-values found between pre- and post-median values are listed.

GROUP A	*pre*	*post*	*Delta*	*p-Value*
cADC	2.495	2.560	0.065	0.0637
mADC	2.225	2.320	0.095	0.0151
cFA	0.1372	0.1368	−0.0004	0.1876
mFA	0.2425	0.2660	0.0235	0.0054

GROUP B	***pre***	***post***	***Delta***	***p-Value***
cADC	2.123	2.235	0.112	0.0016
mADC	1.928	2.045	0.117	0.0001
cFA	0.1208	0.1378	0.0170	0.0104
mFA	0.1995	0.2328	0.0333	0.0001

Median values for ADC are expressed as $\times 10^{-3}$.
*Statistically significant correlation (p-value < 0.05).

after diuretic stimulation are reported in Table 2. For group A, Wilcoxon matched pairs signed rank test revealed no statistically significant difference between pre- and post-furosemide cADC values ($p > 0.05$), and between pre- and post-furosemide cFA values ($p > 0.05$); a statistically significant difference was found comparing pre- and post-mADC values ($p = 0.0151$), and also between pre- and post-mFA values ($p = 0.0054$).

Considering group B, Wilcoxon matched pairs signed rank test revealed a statistically significant difference between all pre- and post-variables, with $p = 0.0016$ for cADC values, $p = 0.0001$ for mADC values, $p = 0.01$ for cFA values, and $p = 0.0001$ for mFA values.

3.3. Pre- and post-furosemide comparison between groups

Box&whiskers plots for cADC and mADC values pre- and post-furosemide are reported in Fig. 3; p values – obtained comparing median values before and after diuretic stimulation – are reported in Table 3.

C-ADC was statistically different between the 2 groups before ($p = 0.002$) and after furosemide ($p = 0.003$) – as shown in Fig. 2a and in Fig. 2b. A statistically significant difference was reported comparing medullary ADC values before and after stimulation, with p values of 0.003 and 0.004 respectively (Fig. 2c and d). Box&whiskers plots for cFA and mFA values pre- and post-furosemide among the two groups are reported in Fig. 3. Considering cortical FA value differences between group A and group B (Figs. 3a-b), there was no statistically significant difference both before and after diuretic administration (p-values respectively 0.179 and 0.731). Medullary FA difference between group A and B was statistically different both before and after furosemide injection, with p-values respectively of 0.004 and 0.042 (Figs. 3c–d).

Table 3
Median values of cortical and medullary ADC and FA before and after diuretic stimulation in Group A and B. The associated p-values – adjusted after Bonferroni-Holm correction – are listed in the last column.

	Median values Group A	Median values Group B	*p*-value
c-ADC pre	2.495	2.123	0.002*
c-ADC post	2.560	2.235	0.003*
m-ADC pre	2.225	1.928	0.003*
m-ADC post	2.320	2.045	0.004*
c-FA pre	0.1372	0.1208	0.179
c-FA post	0.1368	0.1378	0.731
m-FA pre	0.2425	0.1945	0.004*
m-FA post	0.2660	0.2328	0.042*

Median values for ADC are expressed as $\times 10^{-3}$. p-values adjusted after Bonferroni-Holm correction
*Statistically significant correlation (p-value < 0.05).

3.4. ROC analysis

For prediction of normal renal function (Group A) using c-ADC values (Fig. 4a and b), ROC analysis showed an Area Under Curve (AUC) of 0.878 (CI = 0.717–0.965) before furosemide – with a sensitivity of 93.3% and a specificity of 68.1% using as threshold a level of 0.0023; after diuretic stimulation, the AUC was slightly lower – 0.856 (CI = 0.690–0.953) – with a sensitivity of 100% and a specificity of 72.2% adopting a threshold level of 0.0023.

Considering ROC analysis for m-ADC values (Fig. 4c), before furosemide AUC was 0.863 (CI = 0.698–0.957), with a sensitivity of 86.7% and a specificity of 77.8% using a threshold level > 0.0021. After diuretic stimulation (Fig. 4d) AUC was 0.835 (CI = 0.665–0.941), with a sensitivity of 93.3% and a specificity of 77.8% using a threshold level > 0.0022.

For prediction of normal renal function (Group A) using c-FA values (Fig. 5a), ROC analysis before furosemide showed an AUC of 0.674 (CI = 0.489–0.826) with sensitivity of 86.75% and specificity of 55.6% using a threshold value > 0.1213; after furosemide, the AUC obtained was 0.535 (CI = 0.354–0.710), with a sensitivity of 80% and a specificity of 50% using a threshold level of > 0.1333 (Fig. 5b).

Considering m-FA values, ROC analysis (Fig. 5c) reported an AUC of 0.848 (CI = 0.681–0.949) before furosemide, with a sensitivity of 80% and a specificity of 88.89% using a threshold level of > 0.2245; after furosemide (Fig. 5d), an AUC of 0.752 (CI = 0.571–0.885) was found, with a sensitivity of 73.3% and a specificity of 83.3% using a threshold level of > 0.2535.

4. Discussion

According to our results, diuretic stimulation increases median values of ADC and FA in the renal medulla. The pharmacological effects of furosemide, which globally improves diffusion and perfusion in kidneys, may explain these increases. It inhibits Na-K-2Cl cotransporters localized in the ascending limb of Henle's loop, and this generates a strong osmotic water drive through tubular structures, diminishing water reabsorption in the descending limb of the medullary loop of Henle [18,19]. Many studies have described similar variations of ADC and FA values in transplanted renal patients. Sigmund et al. evaluated the changes of ADC values after hydration and furosemide in a population of healthy kidneys: on baseline acquisitions, they found that cortical and medullary ADC values were $2.40 \times 10^{-3}\,mm^2/s$ and $2.25 \times 10^{-3}\,mm^2/s$ respectively. After furosemide, an increase of ADC values was reported both for cortical and medullary regions, with values of $2.48 \times 10^{-3}\,mm^2/s$ and $2.34 \times 10^{-3}\,mm^2/s$ respectively [19].

In our study, ADC and FA values of transplanted renal recipients were similar to those reported by Hueper et al. [16], and after furosemide their changes were very similar to those described by Sigmund et al. [19]. More in detail, furosemide also increased medullary anisotropy significantly in both groups: pre- and post-stimulation median mFA values were respectively 0.2425 and 0.2660 in group A, and 0.1995 and 0.2328 in group B.

Diffusion MRI may potentially allow for differentiation between normal and impaired renal function: cADC values of group A were significantly higher than those of group B; however, this difference decreased after diuretic stimulation. Comparing the two groups, the p values were 0.002 and 0.003 – respectively before and after diuretic administration; therefore, the diuretic stimulation seems to slightly reduce the capability of diffusion MRI in differentiating the function of normal and abnormal transplanted kidneys. Also for mFA, the statistical difference between the two groups was reduced after diuretic stimulation, showing a p value of 0.004 before stimulation, and a p value of 0.042 after furosemide.

Our results showed that cortical mean ADC values are higher than

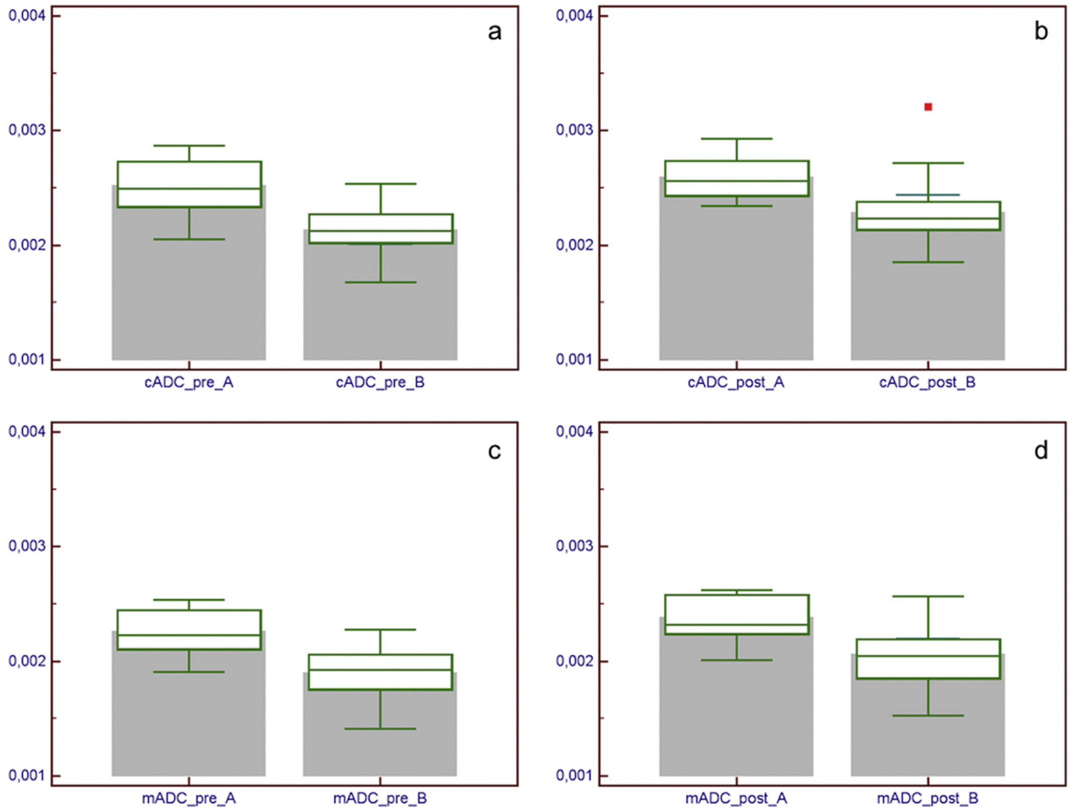

Fig. 2. Box and whiskers plots pre- and post-furosemide for cortical ADC (figures a and b) and medullary ADC (figures c and d) values.

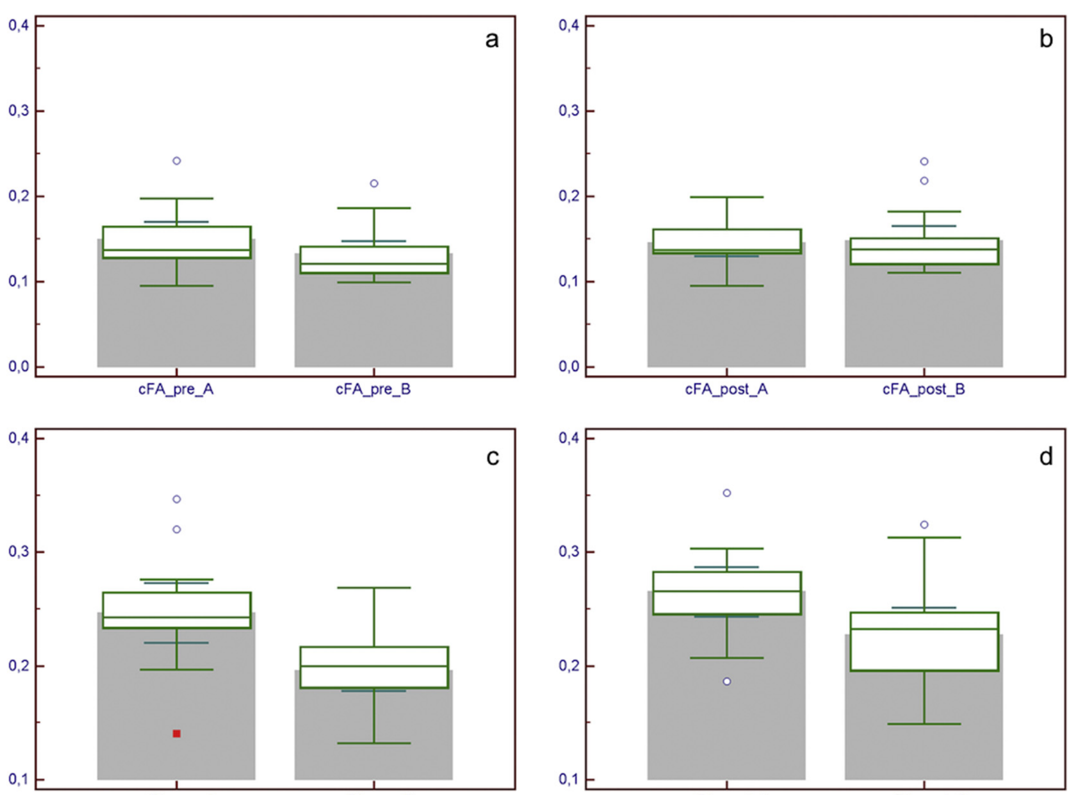

Fig. 3. Box and whiskers plots pre- and post-furosemide for cortical FA (Figures a and b) and medullary FA (figures c and d) values.

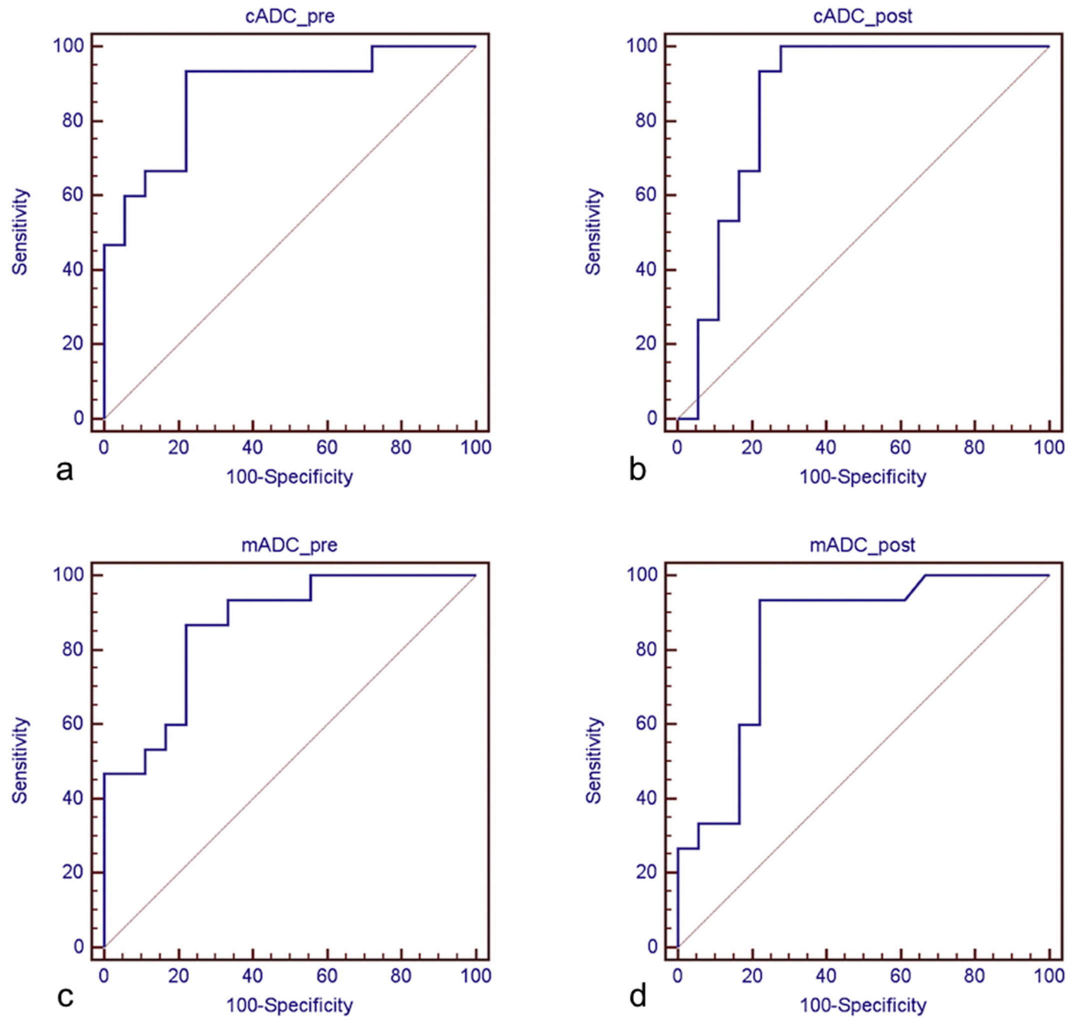

Fig. 4. Receiver operating curves (ROC) for c-ADC and m-ADC, pre- and post-furosemide administration. The ROC curve of figure a shows an AUC of 0.878, which means a sensitivity of 93.3% and a specificity of 68.1% using a threshold c-ADC level of 0.0023. Post-furosemide, the ROC curve shows an AUC of 0.856, with a sensitivity of 100% and a specificity of 72.2% using a threshold c-ADC level of 0.0023 (Fig. 4b). In figure c, the pre-furosemide ROC curve shows an AUC of 0.863, with a sensitivity of 86.7% and a specificity of 77.8% using a threshold level of 0.0021. The ROC curve for post-furosemide m-ADC shows an AUC of 0.835, with a sensitivity of 93.3% and a specificity of 77.8% using a threshold level of 0.0022 (Fig. 4d).

medullary ones, before and after diuretic stimulation: these results agree with previous findings already reported in literature. Indeed, cortical regions have higher blood volume and large tubular diameters [19,21,22], and this explains their higher values. The ADC difference between cortical and medullary regions is reduced in transplanted kidneys: before furosemide, we found difference values of 0.27×10^{-3} for group A and 0.195×10^{-3} for group B. After stimulation, these difference values were 0.24×10^{-3} (group A) and 0.19×10^{-3} (group B). The loss of cortical-medullary difference has been explained by the lack of autonomic innervation in transplanted kidneys and by the increase of perfusion and flow effect along tubules [4].

One of the most important limitations of using diffusion MRI in the evaluation of renal activity is the overlap of ADC and FA values comparing different groups. Based on our results, certainly limited due to the low number of patients, furosemide is perhaps an unreliable diagnostic tool to reduce overlap of ADC and FA values among transplanted kidney recipients with different levels of renal function. Several cut-off values have been suggested to stratify patients according to their function; more specifically, a previous paper suggested that an ADC value of 2.08×10^{-3} may predict normal renal function with a sensitivity of 92.3% and a specificity of 68.2% [23]. To predict impaired renal function, a threshold ADC value of $< 2.07 \times 10^{-3}$ may be used with a sensitivity and specificity of 83.3% and 82.6% [23]. However, a certain degree of overlap has been reported. A combination of Intravoxel Incoherent Motion (IVIM) and Arterial Spin Labeling (ASL) has been recently suggested to better investigate diffusion and perfusion properties for allografts: a higher area under the ROC curve (0.865) was observed combining IVIM and ASL [24].

The AUC values observed in our analysis were slightly lower after diuretic stimulation; therefore, other functional applications should be found to better stratify ADC and FA values among groups. Renal transplant recipients – with lower creatinine clearance values – showed a good response to diuretic stimulation; however, this seems to be in contrast with what has been previously reported in literature. In a previous paper by Smith et al. [25], non-responder recipients showed reduced plasma clearance, renal clearance and renal clearance to creatinine clearance ratio; non-responders have less ability to secrete furosemide into tubular fluid [25]. The slightly better response – observed in our study for ADC and FA in group B – does not have a clear explanation; probably, subjects with a higher amount of interstitial edema in the renal parenchyma show a more powerful diuretic response, increasing fluid urine output. The medullary differences of ADC and FA values decreased more after furosemide, which means that it offers an opportunity to partially recover renal function when damaged. These data indirectly could confirm that injuries occur predominantly in medullary regions, reducing anisotropy and diffusion water motion.

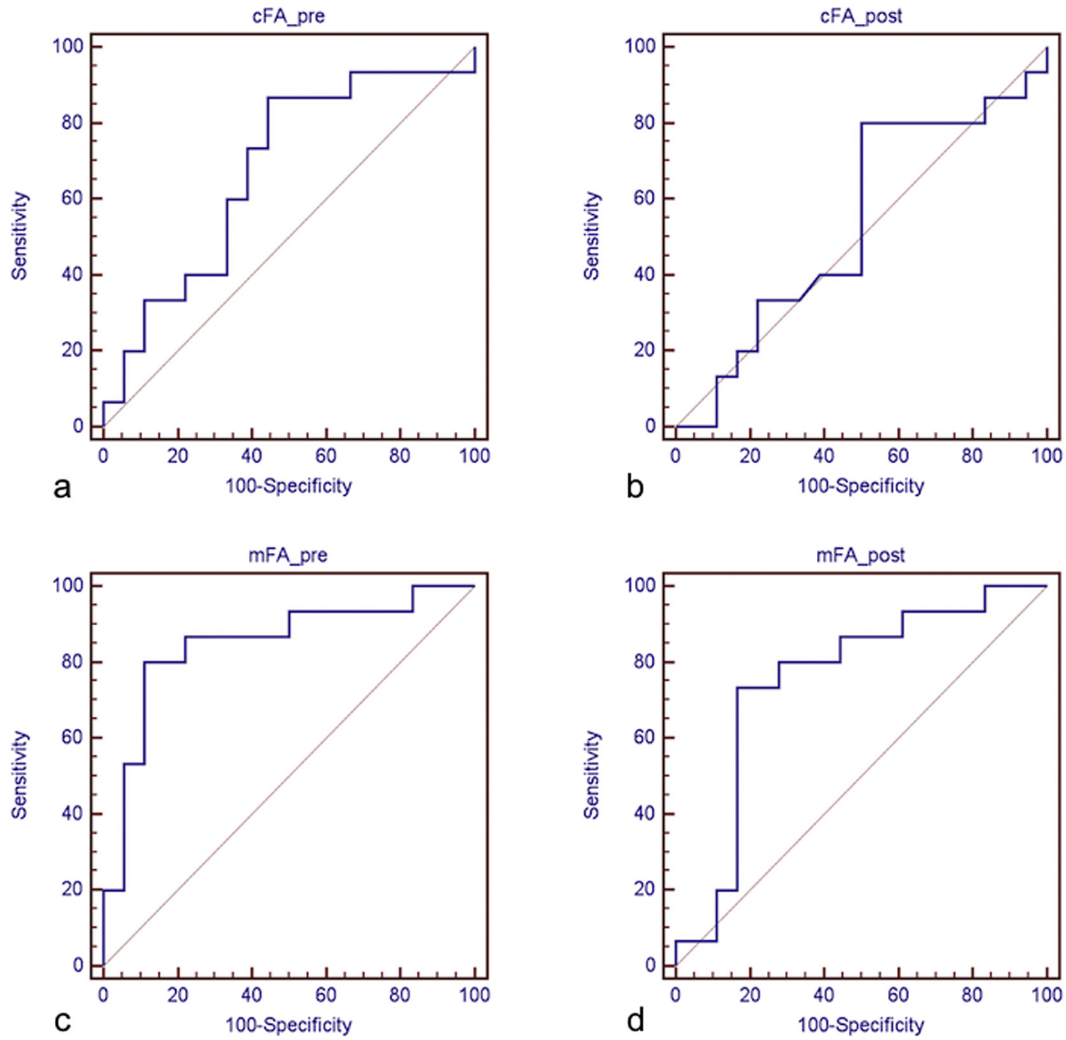

Fig. 5. ROC curve for c-FA and m-FA, pre- and post-diuretic stimulation. In figure a (pre-diuretic stimulation), ROC analysis shows an AUC of 0.674, with a sensitivity of 86.75% and a specificity of 55.6% using a threshold c-FA level of 0.1213; post furosemide, the ROC curve shows an AUC of 0.535, with a sensitivity of 80% and a specificity of 50% using a threshold c-FA level of 0.1333 (Fig. 5b). In figure c (before furosemide), the curve shows an AUC of 0.848, with a sensitivity of 80% and a specificity of 88.9% using a threshold m-FA level of 0.2245. After furosemide (figure d), the ROC curve shows an AUC of 0.752 with a sensitivity of 73.3% and a specificity of 83.3% using a threshold m-FA level of > 0.2535.

Several mechanisms have been proposed: fibrosis, increased tubular pressure and edema could reduce interstitial spaces, damaging tubular orientation and renal architecture.

Our study has several limitations. Mainly, we did not investigate a large number of patients: the analysis was performed on a sample of 33 renal recipients. Patients were also investigated without any recommendations or suggestions for hydration in the days before examinations, and this could be considered a potential bias; ideally, in a future study, a standard hydration protocol and specific diet restrictions should be adopted in order to evaluate a more homogeneous patient cohort. In addition, no histopathologic correlation was available for our transplanted kidneys: as a consequence, we are not able to investigate renal tissue, particularly in subjects with impaired renal function.

In conclusion, based on our results, furosemide seems not to reduce the overlap among FA and ADC values in different renal recipients: functional indexes appear more similar after diuretic stimulation. The use of diuretic stimulation – to better delineate functioning and non-functioning renal recipients – seems not to be very useful in clinical practice – even if our results have been reported in a very small cohort of patients. Medullary FA was the best diagnostic tool in differentiating normal and impaired renal function in a population of transplanted renal recipients. Further studies are needed to better investigate the relationship between furosemide administration and variation of functional indexes (ADC and FA), and to validate the use of diuretic stimulation as a diagnostic tool in functional MR using DWI and DTI.

Funding

No funding was received.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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