ASSESSMENT OF THE TRANSPLANTED KIDNEY USING DIFFUSION TENSOR IMAGING

VYŠETŘENÍ TRANSPLANTOVANÉ LEDVINY ZOBRAZENÍM TENZORŮ DIFUZE

original article

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Accepted: 15. 5. 2009.

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The study was supported by the research project MSM-0021620819 of the Czech Government.

SUMMARY

Ferda J, Mirka H, Reischig T, Hes O, Kreuzberg B. Assessment of the transplanted kidney using diffusion tensor imaging

Aim. To compare the diffusion parameters of the renal medulla and cortex and to evaluate the possibilities of the diffusion tensor imaging (DTI) in the assessment of the transplanted kidney allograft (TXK).
Method. 19 patients (13 males, 6 females, mean age 42.2 y) underwent DTI of TXK 12 hours before the biopsy after written consent; the study was approved by the local ethics committee. The imaging protocol contained a half-Fourier single shot T2 weighted sequence (HASTE) to plan 12-directional diffusion weighted sequence with b = 500 sec/mm^2 and b = 0 sec/mm^2. A DTI software package (produced by General Hospital Corporation, Boston, MA, USA) was used for calculation of apparent diffusion coefficient (ADC) and fraction anisotropy (FA) separately in the medulla and cortex. ADC and FA of the medulla and cortex within the same kidney were compared using a paired t-test. Two subgroups according to the biopsy finding, normal (n = 9) and pathologic (n = 10), were tested using the Wilcoxon-White test to find differences in ADC, FA, ADC medulla/cortex ratio and FA medulla/cortex ratio.
Results. A significant difference ($p < 0.001$) was found in FA between the medulla and cortex, but no difference between ADC values. FA values of the medulla aided to identify TXK affected by tubulointerstitial rejection ($p = 0.05$). Significant differences of the FA medulla/cortex ratio of ($p < 0.001$) and FA of the medulla ($p = 0.05$) were found between tested subgroups. Other differences were statistically insignificant.
Conclusion. The medulla differs from the cortex in FA values. The FA medulla/cortex

SOUHRN

Ferda J, Mirka H, Reischig T, Hes O, Kreuzberg B. Vyšetření transplantované ledviny zobrazením tenzorů difuze

Cíl. Porovnat parametry difuze ve dření ledviny a v její kůře a dále zhodnotit možnosti zobrazení tenzorů difuze (DTI) v posuzování transplantované ledviny
Metoda. Devatenáct pacientů (13 mužů a 6 žen, průměrný věk 42,2 let) podstoupilo DTI 12 hodin před provedením biopsie transplantované ledviny, studie byla schválena lokální etickou komisí. Vyšetření zahrnovalo zobrazení T2 váženou sekvencí (HASTE) k naplánování difuzního zobrazení ve 12 nonkolineárních směrech s parametry b = 500s/mm^2 a b = 0 s/mm^2. K vyhodnocení vyšetření byl použit DTI software (General Hospital Corporation, Boston, MA, USA), který umožnil hodnocení aparentního difuzního koeficientu (ADC) a frakční anisotropie (FA) odděleně v kůře a v dřeni ledviny. Hodnoty ADC a FA v dané ledvině byly porovnány a vzájemně v souboru hodnoceny pomocí párového t-testu. Dvě podskupiny ledviny normálních dle histologie (9 ledvin) a patologických (10 ledvin) byly testovány Wilcoxonovým-Whiteovým testem tak, aby byly nalezeny rozdíly mezi ADC, FA a dále poměry obou parametrů mezi korou a dření.
Výsledky. Signifikantní rozdíl ($p < 0,001$) byl nalezen v souboru všech ledvin mezi hodnotami FA ve dřeni a v kůře; statisticky významný rozdíl v ADC nebyl nalezen. FA pomohl identifikovat tubuloitersticiální rejekci ($p = 0,05$). Signifikantní rozdíly mezi FA poměrem medulla/cortex ($p < 0,001$) a FA medulla ($p = 0,05$) byly nalezeny mezi normálními a patologickými nálezy na ledvinách. Ostatní rozdíly byly statisticky nevýznamné.
Závěr. Dřeň a kůra ledviny se významně liší v hodnotách frakční anizotropie. Poměr FA

ratio is a promising parameter in the assessment of the normal or pathological allograft.
Key words: kidney transplantation, magnetic resonance imaging, diffusion tensor imaging, rejection.

mezi dření a korou je slibným parametrem k odlišení normálního od patologicky změněné transplantátu ledviny.
Klíčová slova: transplantace ledviny, magnetická rezonance, diffusion tensor imaging, rejekce.

INTRODUCTION

Diffusion weighted magnetic resonance imaging appears to be promising as a noninvasive approach in detection of the molecular mobility changes in living tissue (1, 2). Current improvements in the imaging of water molecules diffusion have been made by the development of more complex diffusion tensor imaging (DTI); it allows directly *in vivo* evaluation of some aspects of tissue microstructure (3–5). While DWI has several clinical applications and is routinely used in investigation of the brain and also solid abdominal organs, especially the liver and pancreas (2, 6, 7), DTI is not routine in most institutions, except for in brain imaging. However, an increased interest in possible clinical applications of DTI for examination of the brain led to intensive research and resulted in several reports; abdominal organs have been considered isotropic structures and are believed to have isotropic diffusion (2, 6–11). Although the ADC value for the kidney is being measured as isotopic diffusion (8–11), only a few authors have reported investigation of the anisotropy in the human kidney (12–14). Similarly to the cerebral white matter, the kidney medulla and the cortex are predominantly formed by tubular structures and the anisotropy of the diffusion reflects the radial structure in the kidney, such as renal vessels and tubules (12).

Precise and early detection of dysfunction after kidney transplantation remains a major challenge for non-invasive imaging methods – we predict that this clinical area in which DTI will be shown will be interesting. The purpose of our study was to prospectively evaluate the feasibility of the diffusion tensor imaging in kidney allograft evaluation and to compare findings with allograft biopsy. Our hypothesis suggested: first – there are differences in diffusion anisotropy between the cortex and medulla in the transplanted kidney; second – most important changes in the transplanted kidney developed at the level of the renal tubular system, so these changes must be reflected in changes of water diffusion anisotropy.

MATERIALS AND METHODS

19 patients (13 males, 6 females, mean age 42.2 y) underwent DTI of transplanted kidney allograft 12 hours before the biopsy. All procedures were performed after written informed consent; the study was approved by the local ethics committee. MR imaging was performed with a 1.5 T scanner (Avanto, Siemens, Erlangen) using a six-channel body coil. For morphologic evaluation and further scanning planning, T2-weighted half-Fourier single-shot images (HASTE – TR 1000 ms, TE 85 ms, flip angle 150°, slice thickness 5 mm) were performed in transversal orientation. For functional diffusion evaluation, the transversal twelve-direction-diffusion weighted images were made using b values of 500 s/mm^2 and 0 s/mm^2 (so called low-b images similar to the T2*-weighted images). The multidirectional diffusion weighted echoplanar sequence was performed with the following parameters: TR 3200 ms, TE 94 ms, 20 sections, 5 mm slice thickness, field of view 350 × 350 mm, matrix 192 × 192, b values 0 and 500 s/mm^2. The gradients were applied in twelve non-collinear directions to maximize the effect of the anisotropy. Spectral saturation was used to minimize the signal of the fatty tissue. A parallel imaging technique (GRAPPA algorithm) with reduction factor of two was applied. Due to the minimal transplanted kidney respiratory motion, respiratory triggering was not used. The total acquisition time was two minutes for the whole procedure.

A DTI software package (produced by General Hospital Corporation, Boston, MA, USA) was used for calculation of apparent diffusion coefficient (ADC) and fraction anisotropy (FA) separately in the medulla and cortex. Measurements were performed in the region with the most pronounced differential signal between the cortex and medulla within four voxels. Positioning of the region of interest was based on low-b images.

MRI examination was performed in the evening; the patient underwent core-cut biopsy of the allograft the next morning. The biopsy was performed under ultrasound guidance. The histo-pathological investigation was performed by a pathologist with 12 years of experience with kidney allograft evaluation.

The ADC and FA of the medulla and cortex within the same kidney were compared using a paired t-test. Two groups, normal and pathologic biopsy findings, were tested using the Wilcoxon-White test to find differences in ADC, FA, ADC medulla/cortex ratio and FA medulla/cortex ratio.

RESULTS

According to the biopsy specimen evaluation, the sample of 19 patients was divided into two groups. The first group of nine

patients consisted of patients with completely normal histology or findings with minimal changes. The second group was formed by a group of ten patients with pathological findings including tubulointerstitial rejection (5 pt.) and cyclosporine toxicity (5 pt.)

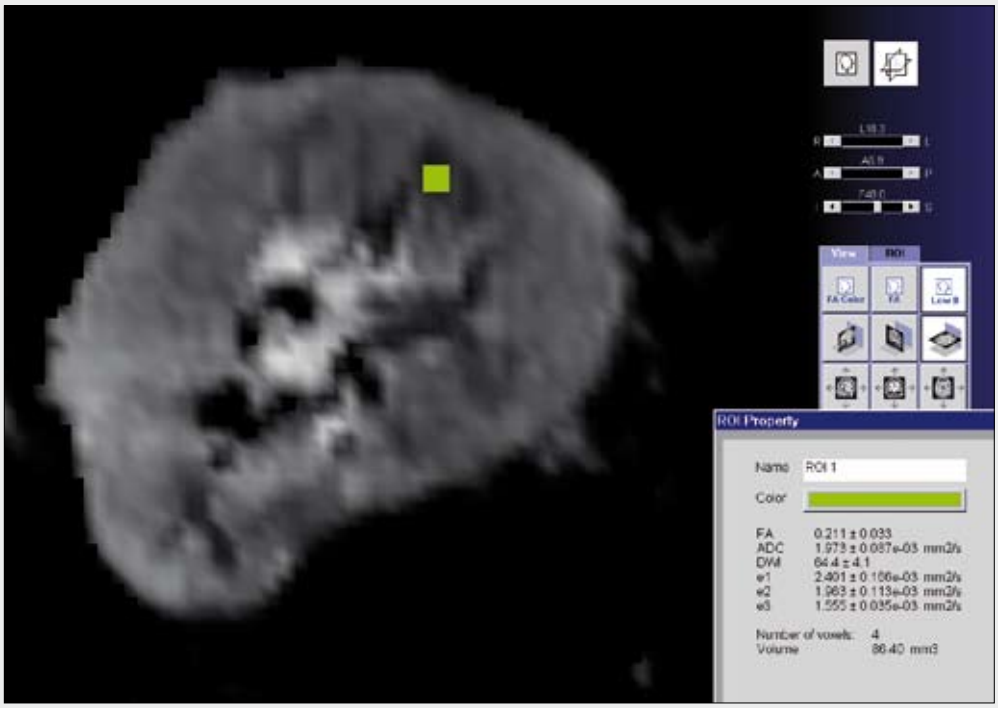
A significant difference ($p < 0.001$) in FA was found between the medulla and cortex, but no difference between ADC values among all of the transplanted allografts. Significant differences of FA medulla/cortex ratio of ($p < 0.001$) and FA of the medulla ($p = 0.05$) were found between the group of patients with normal kidneys (9 patients) and the group of patients with pathologic findings. The FA values in the medulla differs significantly from the others ($p = 0.05$). The rest of the differences in parameters – ADC and ADC medulla/cortex ratio – were statistically insignificant.

DISCUSSION

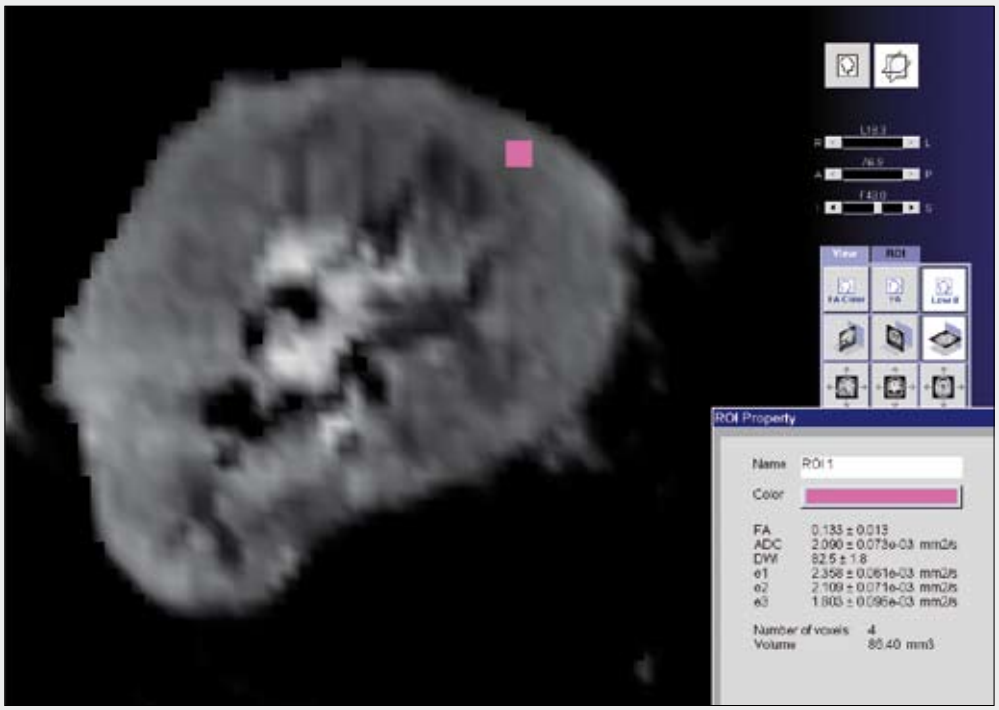
Diffusion-weighted imaging (DWI) is a well established method implemented in many routine protocols, especially in brain imaging protocols. Diffusion weighted magnetic resonance imaging appears to be promising as a noninvasive approach in evaluation of the changes in tissue microstructure. It shows the mobility of water and enables detection of early signs of brain ischemia, but it is also increasingly used in assessments of other brain diseases, e.g. brain tumors, multiple sclerosis and others. By taking advantage of the intrinsic directionality of water molecules, Brownian motion, DTI yields quantitative measures reflecting the integrity of the tubular structures. When water molecules are unconstrained the direction of motion of a given molecule is random (1, 3–5). Diffusion

Table 1. ***Study population, biopsy and DTI results***
Tab. 1. ***Skupina pacientů, biopsie a DTI výsledky***

Sex	Age	Histology	Medulla FA	Medulla ADC	Cortex FA	Cortex ADC	Medulla/cortex FA ratio	Medulla/cortex ADC ratio
female	28	normal finding	0,455	2,578	0,154	2,611	2,955	0,987
male	39	normal finding	0,474	2,173	0,250	1,988	1,896	1,093
male	44	normal finding	0,360	2,072	0,133	2,166	2,707	0,957
male	57	normal finding	0,266	1,909	0,081	2,133	3,284	0,895
female	20	minimal changes	0,401	2,765	0,136	2,004	2,949	1,380
male	38	minimal changes	0,357	2,569	0,180	2,508	1,983	1,024
male	42	minimal changes	0,362	2,109	0,155	2,326	2,335	0,907
female	55	minimal changes	0,319	1,735	0,210	1,628	1,519	1,066
male	55	minimal changes	0,405	2,563	0,169	2,691	2,396	0,952
male	41	cyclosporin toxicity	0,354	2,359	0,122	2,156	2,902	1,094
male	43	cyclosporin toxicity	0,321	1,894	0,111	2,075	2,892	0,913
male	44	cyclosporin toxicity	0,265	2,769	0,179	2,77	1,480	1,000
female	52	cyclosporin toxicity	0,346	2,4	0,232	2,369	1,491	1,013
male	63	cyclosporin toxicity	0,296	1,621	0,199	2,012	1,487	0,806
female	31	tubulointerstitial rejection	0,218	1,863	0,287	1,997	0,760	0,933
male	31	tubulointerstitial rejection	0,352	1,91	0,156	2,167	2,256	0,881
male	38	tubulointerstitial rejection	0,295	5,566	0,808	8,441	0,365	0,659
male	38	tubulointerstitial rejection	0,344	2,116	0,187	2,401	1,840	0,881
male	43	tubulointerstitial rejection	0,281	1,578	0,193	1,578	1,456	1,000



◀ *Obr. 1A*

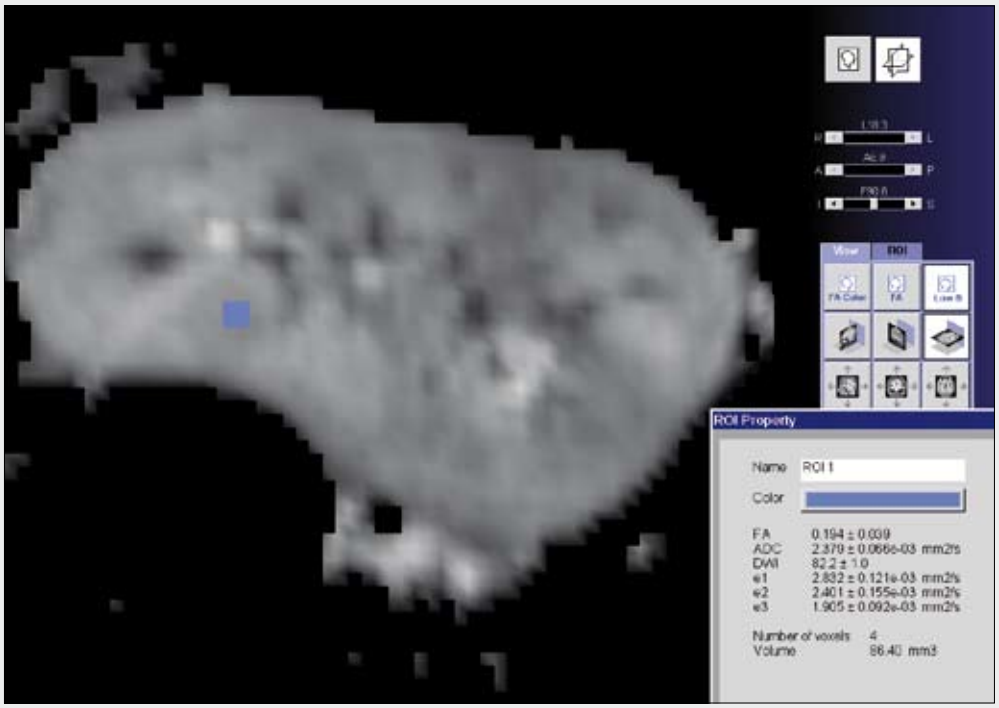


◀ *Obr. 1B*

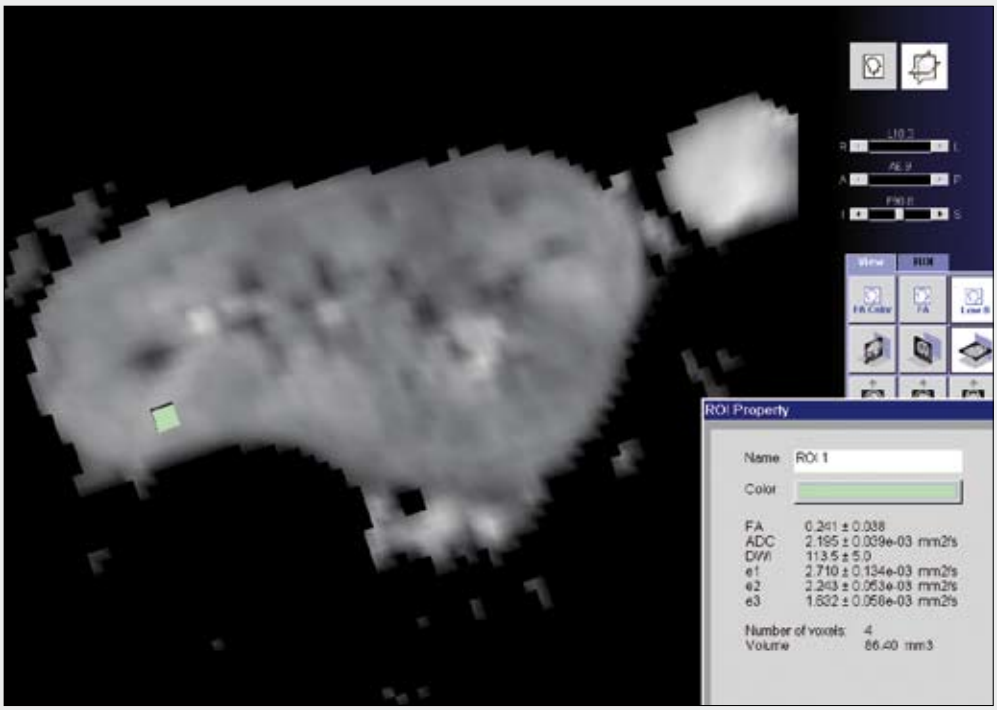
Fig. 1. ***Transplanted kidney allograft, histology revealed normal tissue, evaluation of the diffusion parameters in medulla (A) and cortex (B)***
Obr. 1. ***Transplantovaná ledvina, histologicky zachycena normální tkáň, hodnocení difuzních parametrů ve dřeni (A) a v kůře (B)***

is referred to as isotropic when motion is equal and unconstrained in all directions (1, 3–5). However, the microstructure of some tissues forms physical boundaries that limit the Brownian motion of molecules, resulting in restriction of the total amount of diffusion. In tissue with a tubular microstructure, the diffusion of water molecules will be relatively more restricted perpendicular to than parallel to the microstructure boundaries and diffusion is then called anisotropic (1, 3–5). Similarly to the brain's white matter, the kidney medulla and the cortex are predominantly formed by tubular structures. Even the hydrophobic myelinated sheath of the white matter fiber is a more effective barrier to free water motion; also the hydrophilic wall of renal tubules are able to constrain motion of the water molecules in several directions.

In DWI, diffusion is described using a scalar parameter, with the diffusion coefficient D. In tissues such as brain gray matter or liver tissue, where the measured apparent diffusivity is isotropic, it is sufficient to describe the diffusion characteristics with a single scalar apparent diffusion coefficient (ADC) (3–5). In tissues with presence of anisotropic diffusion, diffu-



◀ Obr. 2A



◀ Obr. 2B

Fig. 2. ***Transplanted kidney allograft, histology revealed tubulointerstitial rejection, evaluation of the diffusion parameters in medulla (A) and cortex (B)***
Obr. 2. ***Transplantovaná ledvina, histologicky zachyceny známky tubulointersticiální rejekce, hodnocení difuzních parametrů ve dřeni (A) a v kůře (B)***

sion can no longer be so characterized, but requires using a tensor which is able to fully describe the amount and directionality of the diffusion. A second order diffusion tensor is the mathematical construct describing anisotropic diffusion including mobility of the water molecules in each direction and the correlation between these directions (5). Since the sensor is symmetric, at least six unique elements are required to fully characterize it (5).

A most common way to describe diffusion including its directionality is calculation of parameters for overall diffusivity and for anisotropy (3–5). The ADC describes overall diffusivity and is derived from the trace of the diffusion tensor. Fraction anisotropy (FA) is a measure of the portion of the diffusion tensor due to anisotropy. For high isotropic media like water or urine the FA tends to be 0. A highly isotropic medium could be characterized by the value tending to be 1 (3–5).

Generally, the ADC value for biological tissue is considered to reflect both diffusion and perfusion, because the random movements in a voxel level include not only molecular diffu-

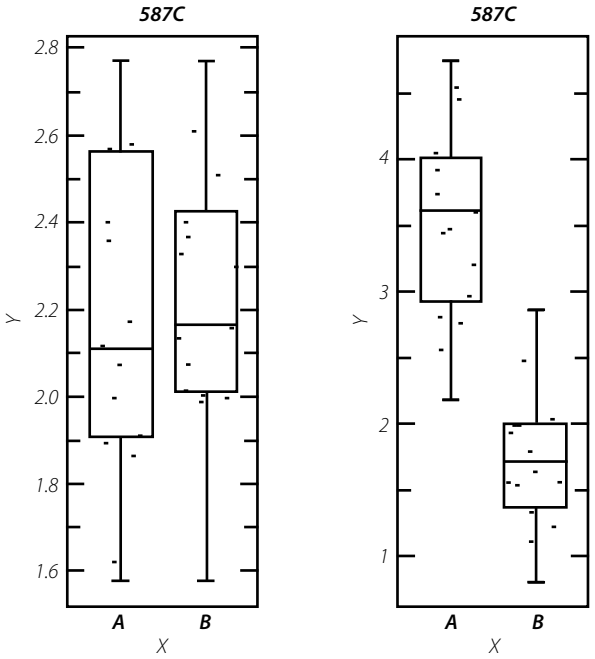
Table 2. ***FA and ADC differences between cortex and medulla, paired t-test***
Tab. 2. ***FA a ADC rozdíly mezi korou a dření, párový t-test***

	FA difference	ADC difference
mean value	0.133	-0.183
t-value	7.328	-0.104
significance	p < 0.001	non-significant

sion of water but also microcirculation (1, 10, 11, 13–15). Diffusion in the kidney is considered to be influenced by the state of hydration (8, 9, 16). When the patients are not restricted in terms of water intake, the diffusion parameters differ inter-individually. DWI has been used to examine transplanted kidneys in animal (15) but also in human studies (11). In the experimental transplanted kidney rejection model, ADC values in the cortex and medulla decreased significantly, suggesting the potential of this method in monitoring early graft rejection (15).

The purpose of our study was to evaluate prospectively the feasibility of the diffusion tensor imaging in kidney allograft assessment and to compare findings with allograft biopsy. To our knowledge, FA values in patients with transplanted kidney allograft have not been reported previously. DTI provides information on diffusion changes in predominantly oriented directions. The value of the diffusion has been discussed and only a few authors reported anisotropy of water diffusion in kidneys (12–14).

Several challenges exist for the application of DTI to the developing changes in the transplanted kidney. Since the main kidney functions are related to migration of the water molecules during glomerular filtration, active or passive tubular secretion and absorption, the evaluation of their diffusion may provide important information about changes in water exchanges in the renal parenchyma. Anisotropy of the diffusion reflects the radial structure in the kidney, such as renal vessels and tubules (12). Both renal compartments, the medulla and the cortex, consist of tubular structures. Ries et al. reported anisotropic diffusion in kidney tissue, higher in the medulla, and statistically important differences in FA between the medulla and the cortex were found (13). However, we observed inter-individual variability in the absolute FA value differences between the medulla and the cortex, the medulla/cortex FA ratio was introduced to define the universal parameter of anisotropy differences in kidney.



▲ Graph 1 ▲ Graph 2

Graph 1. ***ADC values in the kidney allograft***
A – medulla; B – cortex
Graf 1. ***ADC – hodnoty v transplantátu***
A – medulla; B – cortex

Graph 2. ***FA values in the kidney allograft***
A – medulla; B – cortex
Graf 2. ***FA hodnoty v transplantátu***
A – medulla; B – cortex

The previously reported findings have found no significant differences between values of ADC in the medulla and cortex within the transplanted kidney (11). Our finding supported the hypothesis that the differences in the tubular structure of kidney medulla and cortex reflect the differences in the directionality of the water molecules motions. Thus, diffusion of the water in the kidney parenchyma appears to be determined, at least in part, by the kidney medulla tubules. We observed a significant difference between FA values in the medulla and cortex; previously reported findings were confirmed (13, 14). Our results supported the idea that the description of

Table 3. ***Detection of the normal kidney allograft, Wilcoxon-White test***
Tab 3. ***Odlišení normálního transplantátu Wilcoxonovým-Whiteovým testem***

Normal allograft	Medulla FA	Medulla ADC	Cortex FA	Cortex ADC	Medulla/cortex FA ratio	Medulla/cortex ADC ratio
u-value	30	16	13	6	32	12
significance	p = 0.05	non-significant	non-significant	non-significant	p < 0.001	non-significant

Table 4. ***Detection of the kidney allograft affected by tubulointerstitial rejection, Wilcoxon-White test***
Tab. 4. ***Odlišení transplantátu s tubulointersticiální rejekcí Wilcoxonovým-Whiteovým testem***

Tubulointerstitial rejection	Medulla FA	Medulla ADC	Cortex FA	Cortex ADC	Medulla/cortex FA ratio	Medulla/cortex ADC ratio
u-value	20	9	20	1	25	9
significance	non-significant	non-significant	non-significant	non-significant	p = 0,05	non-significant

the water diffusion must be based on tensor imaging not on only scalar values of apparent diffusion coefficient.

The changes in water mobility were reported in edematous brain tissue (5, 17), similarly developed in the kidney on the cellular microstructure level. The cellular swelling and extracelullar edema in pathological conditions in kidney medulla during tubulointerstitial rejection constrains the free water motions inside the tubules and diminishes the pronounced diffusion anisotropy. The other principle of FA reduction is worsening of the free migration across the tubular wall cells due to intracellular edema. According to the microcirculation influence on diffusion weighted images, decreased perfusion might have influence on the diffusion isotropy. These facts could play the main role in changes of the diffusion anisotropy (10–12) in kidney tissue and might aid in distinguishing normal or dysfunctional kidney allograft.

There were limitations to our study. First, histo-pathological findings in the group of the dysfunctional allografts were inhomogeneous. Second, the correlations between the post-transplantation time and age of the kidney donor were not assessed. Third, the reproducibility of the measurements could be different, when the larger areas of measurement were used.

There are also some problems in data acquisition. The main artifacts in DTI data are the usual artifacts and problems associated with acquiring DWI data from which the diffusion tensor is estimated. Multiple causes of the artifacts include data misregistration due to eddy currents, ghosting due motion artifacts, chemical shift artifacts and signal loss due to susceptibility variability. Image quality improvements were enabled using the integrated parallel acquisition technique, which allows obtaining images with reduced distortion. Although the transplanted kidney was moving during shallow breathing, we had no problems with motion artifacts and the respiratory triggering could be omitted (11–14).

In conclusion, DTI of the transplanted kidney yields information on kidney medulla microstructure, as exemplified here in kidney allograft. DTI of the transplanted kidneys provided the examination method, probably useful in detection of the normal or pathological condition of the allograft. However, to evaluate the potential of the diffusion tensor imaging in the assessment of the morphological derangements in patients with renal allografts, larger studies must be arranged, and these studies should be linked with volume analysis of the diffusion parameters within the medulla and cortex of the transplanted kidney.

LITERATURA

1. **Stejskal EO.** Use of spin echoes in a pulsed magnetic-field gradient to study anisotropic, restricted diffusion and flow. J Chem Phys 1965; 43: 3597–3603.
2. **Yamada I, Aung W, Himeno Y, Nagawa T, Shibuya H.** Diffusion coefficients in abdominal organs and hepatic leasions: evaluation incoherent motion echo-planar MR imaging. Radiology 1999; 210: 617–623.
3. **Hajnal JV, Doran M, Hall AS, et al.** MR imaging of anisotropically restricted diffusion of water in the nervous system: technical, anatomic and pathologic considerations. J Comput Assist Tomogr 1991; 15: 1–18.
4. **Pierpaoli C, Basser PJ.** Toward a guantitative assessment of diffusion anisotropy. Magn Reson Med 1996; 36: 893–906.
5. **Sorensen A, Wu O, Copen W, et al.** human acute cerebral ischemia: detection of changes in water diffusion anisotropy by using MR imaging. Radiology 1999; 212: 785–792.
6. **Ichikawa T, Erturk SM, Motosugi U, Sou H, Iino H, Araki T, Fujii H.** High-b value diffusion-weighted MRI in colorectal cancer. AJR 2006; 187: 181–184.
7. **Ichikawa T, Erturk SM, Motosugi U, Sou H, Iino H, Araki T, Fujii H.** High-b value diffusion-weighted MRI for detecting pancreatic adenocarcinoma: preliminary results. AJR 2007; 188: 409–414.
8. **Namimoto T, Yamashita Y, Mitsuzaki K, Nakayama Y, Tang Y, Takahashi M.** Measurement of the apparent diffusion coefficient in diffuse renal disease by diffusion weighted echo-planar MR imaging. J Magn Reson Imaging 1999; 9: 832–837.
9. **Müller MF, Prasad PV, Bimmler D, Kaiser A, Edelman RR.** Functional imaging of the kidney by measurement of the apparent diffusion coefficient. Radiology 1994; 193: 711–715.
10. **Thoeny HC, De Kreyzer F, Oyen RH, Peeters RR.** Diffusion weighted MR imaging of kidneys in healthy volunteers and patients with parenchymal diseases: initial experience. Radiology 2005; 235: 911–917.
11. **Thoeny HC, Zumstein D, Simon-Zoula S, et al.** Functional evaluation of transplanted kidneys with diffusion-weighted and BOLD MR imaging: initial experience. Radiology 2006; 241: 812–821.
12. **Fukuda Y, Ohashi I, Hanafusa K, et al.** Anisotropic diffusion in kidney: apparent diffusion coefficient measurements for clinical use. J Magn Reson Imaging 2000; 11: 156–160.
13. **Ries M, Jones RA, Basseau F, Moonen CT, Grenier N.** Diffusion tensor imaging of the human kidney. J Magn Reson Imaging 2001; 14: 42–49.
14. **Ries M, Basseau F, Tynda B, et al.** Renal diffusion and BOLD MRI in experimental diabetic nephropathy. J Magn Reson Imaging 2003; 17: 104–113.
15. **Yang D, Ye Q, Williams DS, Hithchens TK, Ho C.** Normal and transplanted rat kidneys: diffusion MR imaging at 7 T. Radiology 2004; 231: 702–709.
16. **Knesplova L, Krestin GP.** Magnetic resonance in the assessment of renal function. Eur Radiol 1998; 8: 201–211.
17. **Morita K, Matsuzawa H, Fujii Y, Tanaka R, Kwee IL, Nakada T.** Diffusion tensor analysis of peritumoral edema using lambda chart analysis indicative of the heterogeneity of the microstructure within edema. J Neurosurg 2005; 102: 336–341.