Assessment of renal allograft function early after transplantation with diffusion tensor imaging

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Aims and objectives

Intense monitoring and early identification of renal allograft dysfunction after kidney transplantation, especially in the early stage, are crucial to allow initiation of appropriate treatment to prevent from serious outcomes. So far, surveillance and follow-up examinations of renal allograft function are mainly based on serum creatinine (SCr), ultrasonography (US) and renal biopsy results. However, all these methods have some deficiencies in detecting early abnormalities of kidney transplant. SCr and US are both insensitive and nonspecific. Renal biopsy with histopathologic assessment is the most effective procedure, but it is invasive, painful and prone to sampling errors (1).

Diffusion weighted imaging (DWI) has been proved to be a promising noninvasive technique for assessment of renal function and pathological changes, and has been already used in native and transplanted kidneys in both human and animal researches (2-8). However, the apparent diffusion coefficient (ADC), which is calculated as a quantitative parameter from DWI, only reflects the properties of global diffusion, but cannot account for the directionality of diffusion. Diffusion is a three-dimension process, which is not necessarily equal in all directions, especially in organized tissues. Healthy kidneys have a well defined structure with radial orientation of tubules, collecting ducts and blood vessels in the medulla, which makes diffusion properties in the medulla demonstrate obvious anisotropy. Diffusion tensor imaging (DTI) provides diffusion measurements in at least six directions. Information obtained from DTI contains not only the amount of diffusion but also the anisotropy of diffusion, which is quantified by the fractional anisotropy (FA), ranged from 0 (no preferred diffusion direction, isotropic diffusion) to 1 (only one diffusion direction, completely anisotropic diffusion). Thus, it can be assumed that DTI is more comprehensive and might be more sensitive to early changes of renal allograft function and microstructure compared to DWI.

For healthy kidneys, FA of the medulla is higher than of the cortex and the reproducibility, repeatability, and low inter-observer, intra-observer variability have been proved in many studies (9-11). In recent years, DTI also has been used in assessing renal damage of chronic parenchymal diseases, diabetic nephropathy and kidney transplant (12-16). However, there is no research focusing on the early stage after transplantation, which is such an important period for allograft recipients. Therefore, the purpose of this study was to evaluate the feasibility of DTI and tractography in assessing renal allograft function early after transplantation and to further investigate the ability of DTI in differentiating allografts with different degrees of function.
Methods and materials

Subjects

This study was approved by our institutional ethical review committee in accordance with institutional guidelines. Written informed consent was obtained from all subjects.

Between March 2012 and February 2013, 51 renal allograft recipients (31 male, 20 female; mean age, 36.7±12.1 years, range: 16-60 years) were included in this study. All allograft recipients received triple immunosuppression therapy based on a combination of calcineurin inhibitors, mycophenolate mofetil and prednisone after transplantation. US was routinely performed before MR examination to exclude hydronephrosis, perirenal fluid collections, and vascular occlusion. The time interval between transplantation and MR examination was 2-3 weeks. For comparison, 26 age-matched healthy volunteers (14 male, 12 female; mean age, 40.5±11.7 years, range: 20-57 years) without any history of renal disease, hypertension, diabetes or other vascular diseases were also included. No specific preparations, such as fasting state or fluid intake restriction, were undertaken before the MR examination.

SCr concentrations were obtained from all renal allograft recipients on the day of MR examination and used to calculate estimated glomerular filtration rate (eGFR) by utilizing the modification of diet in renal disease (MDRD) formula (15). According to the National Kidney Foundation Disease Outcomes Quality Initiative guidelines (17) and the calculated eGFR, all subjects were divided into four groups: group A, healthy volunteers (n=26); group B, recipients with good or stable function (eGFR#60 ml/min/1.73m², n=24); group C, recipients with moderately impaired allograft function (30#eGFR#60 ml/min/1.73m², n=19); group D, recipients with severely impaired allograft function (eGFR #30 ml/min/1.73m² , n=8).

MR Imaging

All subjects were examined with a clinical 3.0T MR scanner (TIM-Trio; Siemens, Erlangen, Germany) with a 32-element surface coil and spine coil integrated into the table. For morphological analysis, axial breath-hold turbo spin-echo T1-weighted images and coronal fat-saturated single-shot spin-echo T2-weighted images were firstly acquired.

DT images were acquired with a fat-saturated oblique-coronal multi-section echo-planar imaging sequence with following parameters: diffusion directions, 6; b values, 0 and 300s/mm²; TR/TE, 1800/103 ms; averages, 9; slices 30; slice thickness, 1.8 mm with no intersection gap; field of view, 230×230 mm²; matrix, 128×128; voxel size, 1.8×1.8×1.8 mm³; parallel imaging acceleration factor, 2. For healthy volunteers, respiratory-triggered
acquisition (trigger delay 1800 ms, respiratory phase expiratory) was used to weaken the impact of respiratory motion. Depending on the frequency of respiratory motion, acquisition time varied from 10 to 15 min. For renal allograft recipients, the respiratory-triggered technique was not applied because respiratory motion artifact was negligible in transplanted kidney owing to their location in the iliac fossa, and the average acquisition time was about 4 min.

**Image analysis**

Images were analyzed by an author (8 years of experience with abdominal MR imaging) who was blinded to all clinical findings. For healthy volunteers, the right kidney was selected for analysis because cardiac and respiratory motion artifacts were relatively limited due to the presence of liver above the right kidney.

The commercially available Neuro 3D software (Siemens Healthcare, Erlangen, Germany) was used for DTI data analysis. Diffusion measurements along 6 axes were defined as the diffusion tensor, to allow a visualization of diffusion properties and directions. The tensor was determined by the eigenvectors (#1, #2 and #3) and eigenvalues (#1, #2 and #3). FA maps were calculated to depict the degree of diffusion anisotropy. ADC maps were calculated on basis of a monoexponential fitting model.

Three sections nearest to the renal hilum were selected for region of interest (ROI) analysis on FA maps. For each selected section, three ellipsoid ROIs of approximately 10-15 pixels were placed in the medulla, and an ROI of 80-120 pixels was manually delineated to cover the renal cortex. These ROIs were simultaneously produced on corresponding ADC maps. The combination of morphologic images, FA maps and ADC maps was used to differentiate cortex and medulla, and to avoid renal vessels and the collecting system. Mean ADC and mean FA values were calculated separately for the cortex and for the medulla.

Tractography was performed by using Diffusion Toolkit software package (version 0.5.2.0) (18). A 3-D whole-kidney tractography was launched with an FA threshold of 0.1 and angle threshold of 60°.

**Statistical analysis**

Mean ADC and mean FA values were expressed as mean±standard deviation. The paired Student’s t test was used to compare diffusion parameters between cortex and medulla within each group. Diffusion parameters between groups were compared by using the one-way analysis of variance (ANOVA) test and the Bonferroni post-test. Pearson correlation coefficients were calculated to analyze the relationship between eGFR and diffusion parameters of renal allografts. Statistical analysis was performed with SPSS 17.0 Software (SPSS Inc., USA). A p-value of less than 0.05 was considered statistically significant.
Furthermore, to test the diagnostic value of diffusion parameters in differentiating allografts with different degrees of function and determine the thresholds, multivariate receiver operating characteristic (ROC) analysis was performed and areas under the curve (AUC) were compared by using Medcalc12.4.0Software (Medcalc Software, Belgium).
Results

Image acquisition was successfully completed in all subjects. Clinical characteristics of subjects are displayed in Table 1.

Table 1 Clinical characteristic of subjects

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=26)</th>
<th>Group B (n=24)</th>
<th>Group C (n=19)</th>
<th>Group D (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.5±11.7 (20-57)</td>
<td>37.0±13.5 (16-57)</td>
<td>42.5±10.7 (24-60)</td>
<td>39.0±15.3 (23-60)</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>14:12</td>
<td>14:10</td>
<td>13:6</td>
<td>4:4</td>
</tr>
<tr>
<td>Time after transplantation (days)</td>
<td>-</td>
<td>16.3±3.2 (14-20)</td>
<td>17.1±2.9 (16-21)</td>
<td>15.5±4.8 (14-21)</td>
</tr>
<tr>
<td>Scr (µmol/L) *</td>
<td>-</td>
<td>92.1±12.6 (72.8-129.2)</td>
<td>152.9±31.8 (92.9-202.0)</td>
<td>465.6±270.7 (238.0-1053.9)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²) *</td>
<td>-</td>
<td>79.2±14.7 (62.9-132.6)</td>
<td>45.5±8.5 (32.4-59.3)</td>
<td>15.5±7.8 (5.21-25.8)</td>
</tr>
</tbody>
</table>

Except the gender, data are mean ± standard deviations. Data in parentheses are ranges.

* Mean eGFR as well as mean SCr were significantly different between groups of allograft recipients (p<0.001 for all).

Characteristics of DT images and tractography

In all healthy volunteers, cortical-medullary discrimination was much clearer in FA maps than in ADC maps. The medulla has higher FA and lower ADC than cortex. 3D whole-kidney tractography illustrated a high number and density of tracts with a distinct radial arrangement. These tracks closely converged into pyramids which matched the anatomical arrangement of the medullary pyramids on FA maps (Fig.1A).

For the allografts, the cortical-medullary discrimination in ADC and FA maps was nearly identical to healthy kidneys in allografts with good function, and decreased along with the severity of the impaired function in groups C and D (Fig.1B-D).
In the allografts with good function, the tractography showed intact tracks as in healthy kidneys (Fig. 1B). However, in the allografts with impaired function, the number and density of tracts significantly decreased along with the severity of the impaired function (Fig.1C-D). There are even many hollow space in the tractography of group D (Fig.1D).

**Fig. 1:** B = 0 images, ADC and FA maps, and whole-kidney tractography of right kidney in a healthy volunteer (A), an allograft with good function (B), an allograft with moderately impaired function (C), and an allograft with severely impaired function (D).

**References:** Tianjin First Center Hospital - Tianjin/CN

*Comparison of diffusion parameters between cortex and medulla*
Cortex had lower FA than medulla in all four groups ($p < 0.001$ for all). Mean ADC of the cortex was significantly higher than of the medulla in group A ($p < 0.001$), but lower in group B ($p < 0.05$). Difference of cortical and medullary ADC was not significant in groups C and D (Table 2).

**Table 2** Comparison of mean FA and ADC ($\times 10^{-3}\text{mm}^2/\text{s}$) between cortex and medulla

<table>
<thead>
<tr>
<th>Group</th>
<th>Cortex Mean FA ($\pm$ Standard Deviation)</th>
<th>Medulla Mean FA ($\pm$ Standard Deviation)</th>
<th>$p$</th>
<th>Cortex Mean ADC ($\times 10^{-3}\text{mm}^2/\text{s}$)</th>
<th>Medulla Mean ADC ($\times 10^{-3}\text{mm}^2/\text{s}$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.32±0.03</td>
<td>0.70±0.05</td>
<td>$&lt;0.001$</td>
<td>2.82±0.19</td>
<td>2.50±0.18</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>B</td>
<td>0.27±0.04</td>
<td>0.67±0.07</td>
<td>$&lt;0.001$</td>
<td>2.94±0.28</td>
<td>3.05±0.45</td>
<td>0.03</td>
</tr>
<tr>
<td>C</td>
<td>0.27±0.03</td>
<td>0.59±0.07</td>
<td>$&lt;0.001$</td>
<td>2.59±0.34</td>
<td>2.56±0.47</td>
<td>0.53</td>
</tr>
<tr>
<td>D</td>
<td>0.25±0.06</td>
<td>0.41±0.07</td>
<td>$&lt;0.001$</td>
<td>1.97±0.30</td>
<td>1.96±0.27</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data are mean $\pm$ standard deviations. Diffusion parameters between in the cortex and in the medulla were compared by using paired Student's $t$ test.

**Comparison of diffusion parameters between groups**

Mean cortical FA were significantly higher in group A than in other three groups ($p<0.001$ for all), while there was no significant difference between the last three groups of allograft recipients (Fig. 2A). For mean medullary FA, cortical ADC and medullary ADC, there was a gradually decreasing trend from group C to D (Fig. 2B-D). The difference between groups A and B was not significant in medullary FA and cortical ADC, but medullary ADC significantly increased from group A to group B (Fig. 2B-D).
Fig. 2: Bar graphs show comparison of cortical FA (A), medullary FA (B), cortical ADC (C) and medullary ADC values (D) comparing between various groups. *P<0.001 compared to Group A, **P<0.001 compared to Group B, #P<0.001 compared to Group C.

**References:** Tianjin First Center Hospital - Tianjin/CN
*Correlation between eGFR and diffusion parameters of allografts*

In renal allografts, there was a significant positive correlation between eGFR and medullary FA ($r=0.812$, $p<0.001$, Fig. 3B), cortical ADC ($r=0.756$, $p<0.001$, Fig. 3C) and medullary ADC ($r=0.757$, $p<0.001$, Fig. 3D). However, there was no linear correlation between eGFR and cortical FA ($p=0.45$, Fig. 3A).
Fig. 3: Scatterplots show cortical FA (A), medullary FA (B), cortical ADC (C) and medullary ADC values (D) plotted with eGFR of renal allograft recipients.

References: Tianjin First Center Hospital - Tianjin/CN
Comparison of differential diagnostic value of diffusion parameters

As medullary FA, cortical ADC and medullary ADC showed strong correlations with eGFR, and all these three diffusion parameters demonstrated significant differences between renal allografts groups, we additionally tested and compared the differential diagnostic value of medullary FA, medullary ADC and cortical ADC for renal allografts with different degrees of function.

ROC curves revealed that medullary FA (AUC=0.792, p<0.001), cortical ADC (AUC=0.818, p<0.001) and medullary ADC (AUC=0.823, p<0.001) all could discriminate groups B and C, and no obvious differences existed between AUCs (p>0.05 for all). The criterion points of medullary FA, cortical ADC and medullary ADC were 0.63 (sensitivity 79.2%, specificity 73.7%), 2.76×10^{-3} mm^2/s (sensitivity 70.8%, specificity 84.2%) and 2.90×10^{-3} mm^2/s (sensitivity 75.0%, specificity 89.5%), respectively (Fig. 4A). As for discrimination between groups C and D, medullary FA (AUC=0.947, p<0.001), cortical ADC (AUC=0.921, p<0.001) and medullary ADC (AUC=0.888, p<0.001) all demonstrated obvious accuracy, and also no significant differences existed between
AUCs ($p > 0.05$ for all). The criterion points of medullary FA, medullary ADC and cortical ADC were 0.50 (sensitivity 84.2%, specificity 100.0%), $2.14 \times 10^{-3}$ mm$^2$/s (sensitivity 100.0%, specificity 75.0%) and $2.03 \times 10^{-3}$ mm$^2$/s (sensitivity 94.7%, specificity 75.0%), respectively (Fig. 4B).

Fig. 4: ROC curves show AUCs (area under curves) of medullary FA, cortical ADC as well as medullary ADC value in differentiating allografts with varied function. (A) Group B vs. Group C; (B) Group C vs. Group D.

References: Tianjin First Center Hospital - Tianjin/CN
Conclusion

Early allograft function is strongly associated with long-term graft survival. In the present study, we performed DTI in kidney transplant recipients in the very early post-transplantation period and demonstrated the feasibility of DTI and tractography to quantitatively and visually evaluate early renal allograft function. By comparison of diffusion parameters in different groups, we found the capability of DTI to quantitatively discriminate healthy kidneys and allografts with varied degrees of function. Poor cortical-medullary differentiation in ADC maps and FA maps as well as loss of the radial arrangement in tractography in allografts with moderately and severely impaired function highlights the ability of DTI to visually and qualitatively detect abnormal changes of microstructure of the allograft.

DTI simultaneously reflects the directionality of diffusion and the magnitude of diffusion, which makes DTI hold a high potential in detecting common acute and chronic pathological impairment of renal function and microstructure. In recent years, DTI has been applied in evaluating functional damage in renal diseases in both human and animals, such as chronic parenchymal diseases, diabetic nephropathy, and ischemic reperfusion injury (13, 14, 19). Previous reports using DTI in renal allograft found a decrease of cortical and medullary ADC and FA in the transplanted allografts, and also reported a correlation of eGFR with medullary FA, cortical and medullary ADC (15, 20). However, the interval between kidney transplantation and DTI examination ranged from several days to more than ten years in the previous studies, which makes patients under heterogeneous clinical circumstances and influences the comparability of DTI data to some extent. In the present study, we performed DTI in a relatively large and homogeneous group of renal allograft recipients. They took DTI examination only 2-3 weeks after kidney transplantation and compared with age-matched healthy volunteers, which makes our results more reliable when evaluating the diagnosis value of DTI at early stage after transplantation. Also, previous study demonstrated that eGFR calculated based on MDRD was an independent predictor for long-term renal transplant survival and was more reliable than SCr (21). So we further divided allograft recipients into three stages according to eGFR, which is more accurate to depict allograft dysfunction compared with previous studies.

Corresponding to previous studies, medulla has higher FA than cortex in both healthy and transplanted kidneys, which probably relates to the radial orientation of tubules, vessels and collecting ducts in the renal medulla (15, 20). Cortex has higher ADC than medulla in healthy kidneys, which is because of the higher perfusion component in the cortex (2, 15, 20). In contrast, cortex has lower ADC than medulla in allografts with good or stable function, but no difference in allografts with moderately and severely impaired function. This finding is similar with the results of Thenoy et al, who assumed it was caused by a loss of autonomic innervation of transplanted kidneys (22).
Many complications such as acute rejection (AR), acute tubular necrosis (ATN), immunological reactions and ischemia reperfusion injury could lead to allograft functional impairment shortly after kidney transplantation. Previous work found that these complications often accompanied with glomerulosclerosis, interstitial fibrosis, tubular atrophy, cellular infiltration at histopathology, and caused a diffusion restriction and a reduction of diffusion anisotropy in kidneys (13, 19). This theory is in line with the results we found that medullary FA, cortical ADC and medullary ADC were significant reduced in allografts with moderately and severely impaired function compared to allografts with good or stable function. Compared with healthy controls, medullary ADC in allografts with good function was even slightly higher. Firstly, it may partly due to the loss of autonomic innervation of transplanted kidneys. Secondly, in our study, ADC values were calculated by a monoexponential model, and the b values (0 and 300 s/mm$^2$) used in DTI imaging protocol were relatively low. Low b values are strongly influenced by perfusion effects, so we hypothesize that the increase is related to the increased perfusion and flow effects along the tubules in allografts with good or stable function (23-25).

There was a significant correlation between eGFR and medullary FA, medullary ADC and cortical ADC of renal allografts, and the correlation for medially FA is comparatively higher. Because of the larger patient population with a larger range of eGFR value, our results showed stronger linear correlation than previous reports (14, 16).

It is the first time to use whole-kidney tractography to visually evaluate the allografts function. Compared to previous reports, this 3D whole-kidney tractography demonstrates a distinct radial pattern of tracks which perfectly matches the histological arrangement of the renal parenchyma, and avoids the bias when choosing the seeds manually (20, 26). It is also the first time to analyze the differential diagnostic efficacies of DTI by using ROC analysis. Medullary FA, cortical ADC and medullary ADC all showed high potential to distinguish allografts with varied degrees of function with regard to the AUCs and the significance level. The differential values of these three parameters showed no obvious divergence. However, the reduction of medullary FA, as well as the corticomedullary difference was more pronounced than the reduction in ADC value, which indicates that DTI is more sensitive than DWI for detection of pathologic changes in allograft microstructure, and medullary FA is the most sensitive parameter.

Some limitations were encountered in this study. First, the underlying pathologic conditions that led to allograft functional impairment were heterogeneous. Thus, the potential for DTI to differentiate between pathologic conditions cannot be derived from our results. Second, we did not standardize the hydration state of subjects. Previous study reported that ADC values calculated during maximum flow of the cardiac cycle were significantly higher than ADC values during minimum flow (27). By using time-resolved electrocardiogram (ECG) triggered DTI to evaluate the impact of renal blood flow on ADC and FA, it is also found that cortical ADC and medullary FA at maximum blood flow were significantly higher than at minimum blood flow (28). Thus, the potential influence
of pulsatile blood flow and hydration state on ADC and FA values has to be considered when interpreting DTI data.

In conclusion, the difference of diffusion parameters between groups with different degrees of function, the reduction of tracts in tractography of kidneys with impaired function, the strong correlation between eGFR and medullary FA, medullary ADC and cortical ADC in allografts all indicate that DTI is a noninvasive approach to quantitatively and visually assess renal allograft function in the early stage after kidney transplantation.


12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new


