

# Multiparametric functional MRI for assessment of acute renal allograft rejection in mice – correlation with renal histology and the composition of T-cell infiltrates

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**Target audience:** Radiologists and physicist with an interest in functional MRI of the kidney and small animal imaging.

**Purpose:** To investigate whether multiparametric functional MRI allows detection of acute renal allograft rejection and to compare MRI parameters with renal histopathology and the composition of cell infiltrates of renal tissue.

**Methods:** An acute renal allograft rejection was induced by allogenic kidney transplantation (ctx) of C57Bl/6-kidneys to Balb/c-mice (n=6). Animals after isogenic ctx (C57Bl/6-kidneys to C57Bl/6-mice) were used as controls (n=5; Figure 1). MRI was performed three weeks after ctx using a 7 Tesla magnet (Bruker, Pharmascan). Renal perfusion was quantified using a flow sensitive alternating inversion recovery (FAIR) EPI ASL sequence (13 TI = 30-8000 ms)<sup>2</sup>. In order to evaluate tissue edema, maps of T1- and T2-relaxation time were calculated. In addition, apparent diffusion coefficients (ADC) were determined from an echoplanar diffusion-weighted sequence (7 b-values = 0-700 s/mm<sup>2</sup>) using a monoexponential fit<sup>3</sup>. After the MRI, animals were sacrificed and histological changes of renal tissue were evaluated according to Banff criteria. Furthermore, the composition of infiltrating cells of renal tissue was assessed by FACS-analysis. Differences between groups of allogenic and isogenic ctx were evaluated using unpaired t-tests and the correlation of functional MRI parameters with the percentage of T-cell infiltrates was determined (Pearson). Values are given as mean±SEM.

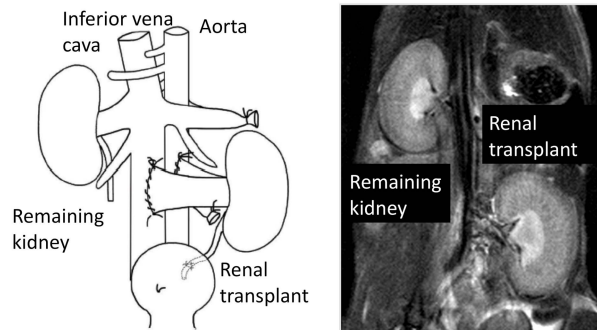
**Results:** Animals after allogenic ctx developed an acute T-cell-mediated rejection according to Banff criteria, whereas renal histology after isogenic ctx was unremarkable. The percentage of infiltrating T-cells was significantly higher after allogenic (38.8±4.0%) than after isogenic ctx (5.5±2.2%; p<0.001). Renal perfusion was significantly impaired in animals with an acute rejection (allogenic ctx) compared to the control group (56±7 vs. 293±44 ml/(min\*100g); p<0.001; Figure 2). T1- and T2-relaxation times of renal tissue were increased after allogenic ctx with most pronounced changes in the outer medulla. Here, T1 values were 1938±53 ms after allogenic and only 1349±27 ms after isogenic ctx (p<0.001). T2 values were 60.1±2.0 ms and 45.7±1.2 ms, respectively (p<0.001). ADC values were significantly reduced after allogenic (1.39±0.14\*10<sup>-3</sup> mm<sup>2</sup>/s) compared to isogenic ctx (1.83±0.05\*10<sup>-3</sup> mm<sup>2</sup>/s; p<0.05). The percentage of T-cell infiltrates negatively correlated with renal perfusion (r=-0.84) and ADC (r=-0.78) and positively with T1- (r=0.97) and T2-relaxation times of renal tissue (r=0.92).

**Discussion:** Functional MRI allows detection of acute, T-cell-mediated renal allograft rejection. This is associated with impairment of renal perfusion, increase of T1- and T2-values, interpreted as tissue edema due to inflammation, and ADC reduction due to cellular infiltration. MRI parameters correlate with the percentage of T-cell infiltrates. Thus, multiparametric functional MRI may improve non-invasive diagnosis of renal allograft rejection.

**References:**

- <sup>1</sup>Rong et al.: A knotless technique for kidney transplantation in the mouse. J Transplant. 2012;127215.
- <sup>2</sup>Hueper et al.: Acute Kidney Injury: Arterial Spin Labeling to Monitor Renal Perfusion Impairment in Mice--Comparison with Histopathologic Results and Renal Function. Radiology. Sept 2013. Epub.
- <sup>3</sup>Hueper et al.: T2 relaxation time and apparent diffusion coefficient for noninvasive assessment of renal pathology after acute kidney injury in mice: comparison with histopathology. Aug 2013. Epub.

**Figure 2:** Maps of renal perfusion, T2-relaxation time and ADC in a control animal after isogenic ctx (upper row) and an animal with acute rejection after allogenic ctx (middle row) are shown. Image level and width is similar for animals after isogenic and allogenic ctx. In the lower row, mean±SEM of functional MRI parameters are depicted and significant differences are indicated. \*p<0.05, \*\*\*p<0.001.



**Figure 1:** The technique for renal transplantation in mice (left; modified according to Rong et al.<sup>1</sup>) and a T2-weighted MRI (right) are shown. The left kidney is removed; the renal transplant is placed in the left lower abdomen and anastomosed to aorta and inferior vena cava. The ureter is implanted into the bladder

