GlucoCEST as method for early detection of renal allograft rejection

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Target audience: Physicists, chemists and radiologists with interest in molecular CEST-MRI and inflammatory processes.

Purpose: Organ transplantation is often accepted as the best treatment both for quality of life and cost effectiveness or is even the only treatment for end state organ failure. Especially kidney transplantation is by far the most frequently carried out solid organ transplantation. However, despite potent immunosuppression, episodes of acute rejection (AR) frequently occur after kidney transplantation [1]. This complication can be treated effectively if diagnosed early. Present screening methods such as elevated serum creatinine, proteinuria, or oliguria lack the desired sensitivity and specificity for early diagnosis of AR as does the "gold-standard", core needle biopsy [1,2]. Non-invasive screening methods assessing the whole graft are needed. Recently, two novel approaches provided new prospects. First, early invading T cells leading to inflammation inside the renal allograft, could be detected by ^{18}F-FDG-PET (^{18}F-fluorodeoxyglucose position emission tomography) due to increased glucose up-take [3,4]. Nonetheless, FDG-PET has limitations, such as renal elimination of the tracer FDG as well as patients' exposure to radiation. Second, it could be shown by MRI that unlabeled D-glucose could be used to detect altered uptake of this sugar in tumor tissue via chemical exchange saturation transfer (glucoCEST)[5,6]. In this study we have implemented glucoCEST-MRI on a rat model of kidney transplantation to test as method for early detection of renal allograft rejection.

Methods: Animal model: Uni-nephrectomized, allogeneically transplanted Lewis rats developing acute allograft rejection after surgery served as the renal transplant model (Lewis Brown Norway F1 to Lewis). In vivo imaging: Six transplanted Lewis rats were investigated by glucoCEST four days post kidney transplantation. *Glucose application:* Immediately before MRI measurements animals received a bolus ip injection of a 1.0 M glucose sterofundin solution (8.5 ml/kg body weight) following a bolus ip injection of a 1.5 M glucose sterofundin solution (4.25 ml/kg body weight) after 30 min. *MRI:* MRI images were acquired at 9.4 T on a Bruker BioSpec94/20 using a 72 mm volume coil. After manual shimming of the region of interest covering both the native and transplanted kidney CEST-spectra were acquired using a respiratory triggered and modified 2D RARE sequence (slice thickness: 1 mm, TE/TR=6.4 ms/5 s, field of view: 47x54 mm^2, Matrix: 128x128, averages: 4, RARE factor: 12) containing a fat suppression and magnetization transfer module (block pulse, t_{sat}=4 s, B_1=1.6 µT, saturation offset range: ± 3 ppm, saturation steps: 0.3 ppm). B_0-mapping and corrections of magnetic field inhomogeneities were performed using WASSR (Water Saturation Shift Reference[7]) using the following saturation parameters: block pulse, tsat=200 ms, B_1=0.5 µT. *GlucoCEST-contrast:* CEST contrast was quantified, calculating the integral from 1.2 ppm to 2.4 ppm of the asymmetric magnetization transfer ratio (MTRsym) curve.

Results and Discussion: To assess kidney rejection by glucoCEST, a glucose infusion protocol was developed and validated. Applying an ip bolus of 1.0 M glucose followed by a second bolus (1.5 M glucose) after 30 min, the blood glucose level was raised by about 120 mg/dl and could be kept constant over the total scan time of approximately 50 min (Fig. 1). In vivo glucoCEST contrast of both the native and the transplanted kidney were calculated and visualized in glucoCEST maps (Fig. 2). Compared to the native kidney, the rejected allograft showed increased CEST-contrast in both the pelvis (native: 0.077 ± 0.039, transplanted: 0.149 ± 0.054, p-value: 0.043) and the cortex (native: 0.026 ± 0.011, transplanted: 0.060 ± 0.027, p-value: 0.033) at day four post transplantation due to increased glucose up-take (Table 1). GlucoCEST contrast changes are probably caused both by the effect of glucose on the CEST signal as well as on T_2 relaxation[8]. In the cortex a similar signal ratio of 1.8 was obtained by ^{18}F-FDG in a previous PET study[4]. Renal rejection in the cortex was confirmed by histology (Fig. 3).

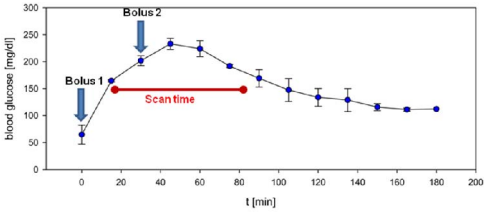

Fig.1: Blood glucose level over time using optimized glucose perfusion protocol

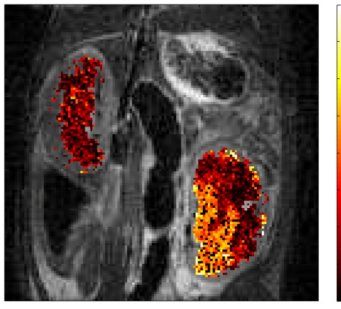

Table 1: CEST contrast ratio of transplanted and native kidney (N=6)	
Cortex	2.3 ± 0.4
Medulla	0.8 ± 0.1
Pelvis	2.1 ± 0.4

Fig.2: Calculated glucoCEST contrast for native kidney (left) and transplanted kidney (right) and corresponding CEST contrast ratios in table 1.

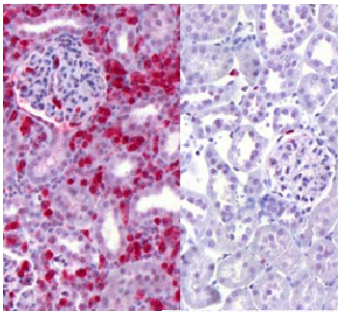

Fig.3: Representative immunohistochemical stainings of CD3-positive T-lymphocytes (red). A significant infiltration pattern was found only in renal allografts undergoing rejection on day 4 post surgery (left) compared with the corresponding healthy control kidney (right).

Conclusion: Significantly different GlucoCEST contrast was detected for native kidneys and renal allografts undergoing rejection. Increased glucose accumulation was identified in the cortex of the transplant due to renal rejection-related inflammation. Our results showed that glucoCEST is a feasible method for early detection of kidney rejection. Thus, glucoCEST may provide a versatile tool to identify and differentiate zones of inflammation in vivo and may add a novel aspect to the field of infection and inflammation MRI.

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