Advanced MRI methods for the differentiation and characterization of acute and chronic kidney diseases in mice

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Background & Aims: The use of MRI for the diagnosis and assessment of acute and chronic kidney diseases includes T1 and T2 weighted techniques, as well as BOLD MRI. Although Contrast-Enhanced MRI (CE-MRI) greatly improves imaging quality of renal pathology – permitting both perfusion imaging and tissue characterization from morphologic enhancement patterns, the incremental benefits from administration of contrast media is limited due to the potential increased risks of worsening renal dysfunction and systemic adverse effects. Therefore, the search for alternative non-invasive imaging methods is crucial. The assessment of renal oxygenation by BOLD MRI was first reported in 1996 by Prasad et al[1]. While BOLD MRI enables tracking changes in organ oxygenation status, we previously demonstrated the feasibility of *Hemodynamic Response Imaging* (*HRI*), an fMRI method combined with transient hypercapnic and hyperoxic challenges, for monitoring changes in liver perfusion and hemodynamics[2], and recently we also established the use of *HRI* for renal perfusion assessment in mice[3]. Moreover we showed the use of True-FISP (characterized by a very high signal-to-noise ratio, with short acquisition times and a T2/T1-weighted image contrast), for sensitively monitoring changes in renal morphology during acute kidney injury in mice (AKI)[3]. The aim of the present study was to assess the utility of these two MRI methods for the differentiation of various renal pathologies, and for evaluating changes in morphology, perfusion and hemodynamics during chronic kidney disease (CKD) in mice.

Methods: CB6F1mice were scanned with a 4.7T MRI Bruker biospec spectrometer once a week during adenine-induced CKD (0.2% adenine in the diet for 4 weeks, n=15) and on days 1, 4, 8, 15 and 22 after AKI induction by intra-muscular glycerol injection (rhabdomyolysis, n=15). True-FISP (TR/TE=3/1.5 ms) images were used to evaluate renal morphology and cortico-medullary differentiation (CMD, the ratio between the cortical and medullary signal intensities, normalized to the adjacent back muscle). *HRI* - T2*-weighted GE (TR/TE=147/10 ms) images were acquired during hypercapnic (5% CO_2) and hyperoxic (95% O_2) challenges as described[2]. Data analysis was performed using IDL software. *HRI* maps are given as the percentage change of signal intensity (ΔS) induced by hypercapnia (ΔSco_2) or hyperoxia (ΔSo_2). Additionally, CE-MRI was performed using T1-weighted GE images (TR/TE=58/5 ms) following administration of Gd-DTPA. Serum urea levels were measured for renal function determination. To examine the degree of fibrosis, Masson-trichrome staining was conducted on kidney sections.

Results: True-FISP images (**Fig.1A top**) during CKD revealed inhomogeneous, patchy pattern of the kidney parenchyma compared to baseline, in accordance with the stripped fibrosis characterizing this model and demonstrated on Masson's Trichrome staining (**Fig.1B**). While during AKI, True-FISP CMD correlated significantly with urea levels, CKD mice showed no change in CMD during the entire study (**Fig.1A top, 1C**), although urea levels were gradually and consistently increasing, reaching maximum of 168 ± 24 mg/dL following 4 weeks of diet. Thus, True-FISP images may assist in distinguishing CKD from AKI. The comparable results from True-FISP and CE-MRI (**Fig.1A bottom**) images, for both CKD and AKI, emphasized the advantages of this method.

HRI maps during CKD progression revealed reduced renal ΔSo_2 values (**Fig.2**), probably reflecting decreased renal perfusion. Whereas the spleen ΔSo_2 values, used as a reference for systemic hemodynamic changes, were found to be increased during CKD progression, in contrast to AKI where ΔS values of the spleen were decreased[3]. This highlights the utility of HRI for non-invasive detection of renal and systemic perfusion changes simultaneously, without the need of contrast-agents. In an additional assay, we tried to establish a model of acute-on-chronic kidney injury, by IM glycerol injection following 4 weeks of adenine-induced CKD. Surprisingly, AKI was not developed in these mice, possibly indicating renal ischemic pre-conditioning.

Conclusions: We present the beneficial use of two non-invasive MRI methods for evaluation of renal pathologies in mice, saving the need for contrast-agent administration. HRI provides supplementary information regarding kidney perfusion and hemodynamics, while True-FISP sensitively tracks morphologic changes, and may further assists in the differentiation of renal pathologies.

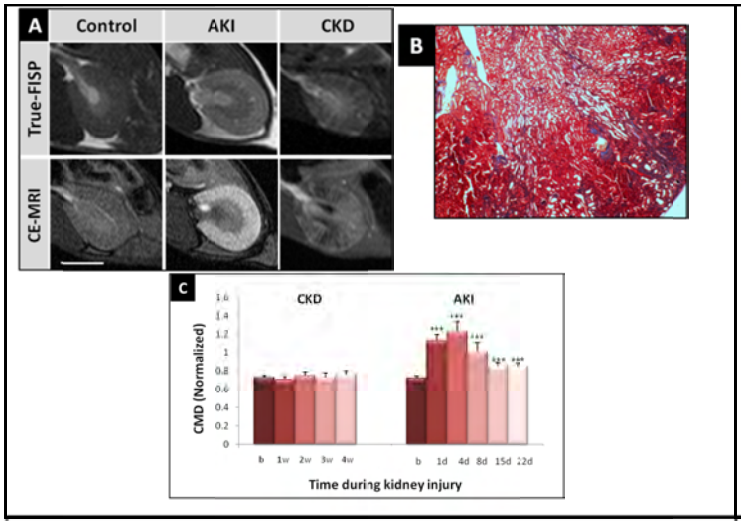

Figure1: **A**- Representative True-FISP (**Top**) and CE-MRI (**Bottom**) images of the left kidney of control (left), AKI (middle) or CKD (right) mouse (bar=1cm). **B**- Representative kidney section from CKD mouse stained with Masson's-Trichrome, demonstrating renal fibrosis. **C**- Mean True-FISP CMD values during CKD or AKI. (n>10; *** p<0.001 compared to baseline).

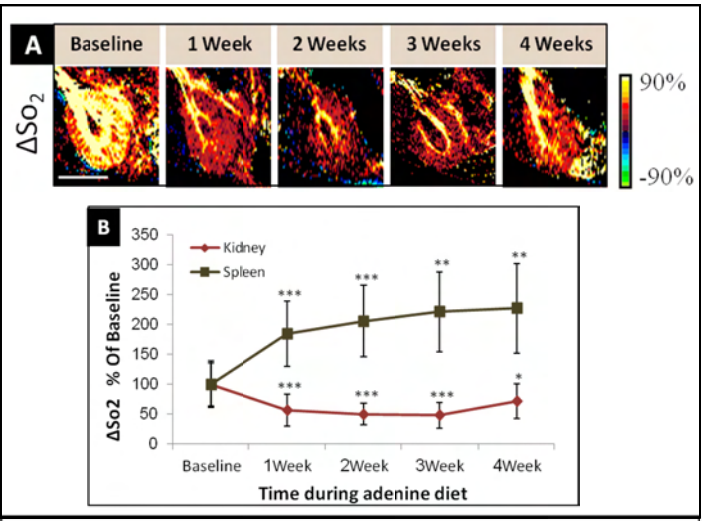

Figure2: **A**- Representative ΔSo_2 *HRI* maps during CKD (color scale bar is located at the right). **B**- Mean ΔSO_2 values calculated from the kidneys and the spleen during CKD. (N>10; * p<0.05, **p<0.01, *** p<0.001 compared to baseline).

References: [1]Prasad PV, Circulation 94: 3271, 1996. [2]Barash H, Radiology 243(3):727, 2007. [3]ISMRM 2011 abstract #2361.