MRI Characterization of Pathophysiological Changes in a Mouse Model of Acute Kidney Injury (AKI)

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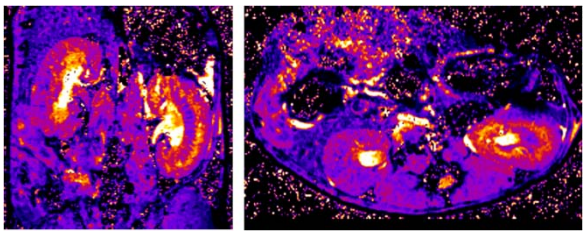
Introduction: Renal medullary hypoperfusion and hypoxia play a key role in acute kidney injury (AKI). The incidence of AKI in hospitalized patients shows an increase of approximately 11% per year [1]. A widely accepted hypothesis is that AKI of various origins share one common link in the pathophysiological chain of events that ultimately leads to AKI: Imbalance between renal medullary oxygen delivery and oxygen demand. Although a variety of methods to assess renal hemodynamics and oxygenation in vivo are established (e.g. blood sampling, ultra-sound flow probes, Laser-Doppler probes, fluorescence-quenching probes), these invasive measurements are limited to short time periods (one experiment) and/or probing only a very small region of the kidney. MRI offers the possibility to assess tissue oxygenation and oedema (via T_2* (BOLD) and T2 contrast respectively) for the whole kidneys, repeatedly and non-invasively. The objective of this work was to demonstrate the feasibility of characterizing alterations in renal hemodynamics and oxygenation under (patho)physiological conditions such as renal ischemia/reperfusion injury (I-R model).

Materials and Methods: ***Animal models.*** We imaged 4 male BL6 mice (weight approx. 20g) in-vivo under isoflurane anesthesia (1.0-2.5% in 50% air / 50% O_2): one naive animal (M1), one animal (M2) 6hrs after a 30-minute ischemia-reperfusion, one animal naive, 6hrs and 24hrs after a severe 30-minute I-R (M3), and one animal 6hrs and 24hrs after a mild 17.5-minute I-R (M4). Experiments complied fully with local institutional ethical and legal requirements. ***MR Imaging.*** Coronal T_2w images and T_2*w images with different echo times were acquired on a 9.4T Bruker Biospec (Ettlingen, Germany) using a four-element mouse cardiac optimized surface coil array. T_2w imaging: RARE (factor 8), TE = 41ms, FOV/mtx/res = 35x30mm/384x196/0.09x0.15mm, 2 slices of 0.3mm thickness. T_2*w mapping: MGE, TE/FA = 3,7,11, 15,19ms/30°, FOV/mtx/res = 35x30mm/256x192/0.14x0.16mm, 2 slices of 0.34mm thickness. TR for both sequences was 900-1200ms (resp. triggered, RARE used flip-back) ***Analysis.*** MGE data were converted to T_2*-maps using the Bruker ISA tool.

Results and Discussion: T_2w and T_2*w images of naïve kidneys and the untouched reference kidneys after unilateral I-R showed the same contrast, while the kidneys that underwent I-R all showed strong changes of contrast in the cortex and medulla (Fig.1): the medulla became darker (T2 decrease), and the cortex brighter (T_2 increase). Even after mild I-R clear changes were observed, which differed from those after a severe I-R and particularly highlighted the cortex-medulla interface. T_2*-mapping showed equally dramatic changes in a more quantitative manner as demonstrated in Fig.2.

Conclusions: Our results suggest that in-vivo MRI characterization of pathophysiological changes in mouse model of AKI is not only feasible but also a rather sensitive method. The future objective of our work is to study renal hemodynamics and oxygenation by means of a new multi-modality approach that combines comprehensive MRI techniques with modern invasive measurements under physiological conditions and in a model of ischemia/reperfusion injury.



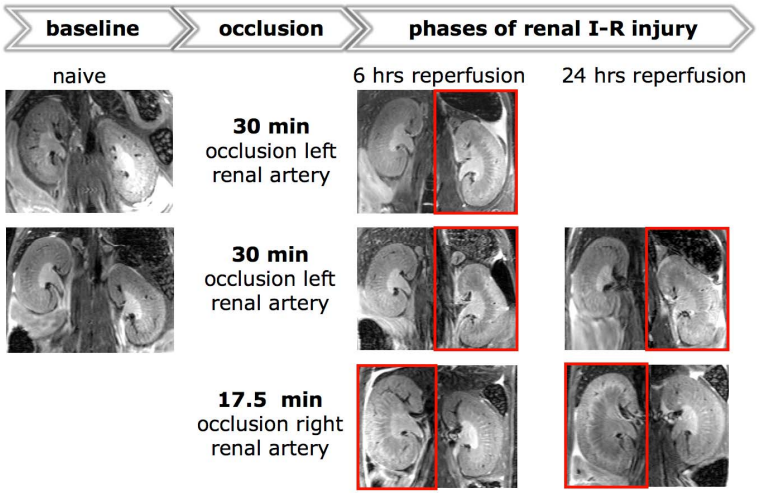


Fig. 1: T_2-weighted images acquired prior **(left)**, after 6 hrs **(middle)** and after 24 hrs **(right)** of unilateral I/R-I (marked in red) using a severe **(top and center)** and mild **(bottom)** I/R mouse model. Images are from animals M1 and M2 **(top row)**, M3 **(middle row)**, and M4 **(bottom row)**. For T_2-weighted imaging a spatial resolution of 0.1x0.15x0.3 mm^3 was accomplished. Strong signal intensity changes were found after ischemia followed by reperfusion. I/R resulted in a T_2 increase in the cortex.

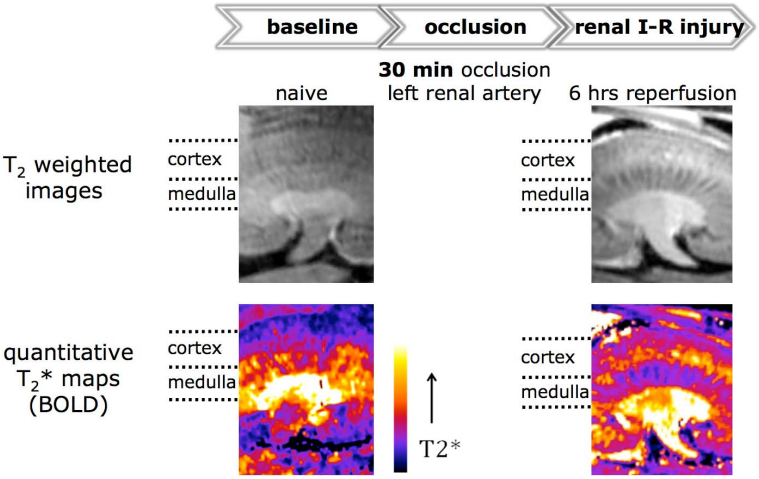


Fig. 2: T_2-weighted images **(top)** and T_2* maps **(bottom)** of a mouse kidney prior **(left)** and after unilateral I/R-I **(right)**. The corticomedullary T_2* gradient observed for normal conditions **(left)** is reversed after I/R-I **(right)**. Images are from animals M1 and M2. **(LEFT):** The corresponding T_2*-maps in axial and coronal view at 6hrs after I-R.

Reference: [1] Xue JL et al. J.Am.Soc.Nephrol. 17:1135-1142, 2006.