Detailing the Relation Between Renal T2* and Renal Tissue pO2 Using a Hybrid and Integrated Approach of Parametric MRI and Invasive Physiological Measurements (MR-PHYSIOL)

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Introduction: Acute kidney injuries of various origins share one common feature in the chain of events: imbalance between kidney medullary oxygen delivery and oxygen demand.[1-4] Quantitative parametric MRI (T_2* mapping) offers a non-invasive approach to probe renal oxygenation but provides rather a surrogate than a quantitative measure of oxygen saturation of hemoglobin. It reflects the oxygenation of blood rather than renal tissue. Changes in tissue pO_2 and T_2* may be closely related but their link is influenced by effects like diffusional O_2 shunting and plasma skimming.[5-7] For a physiological interpretation of T_2* a calibration using an integrative approach that combines parametric MR with physiological measurements is prudent if not essential.[4] To this end this work employs an integrative hybrid approach that combines established invasive but quantitative techniques (renal perfusion pressure, renal blood flow, local blood flux and tissue pO_2) with a 9.4 Tesla small animal MR system (MR-PHYSIOL)[8] with the ultimate goal to detail the relation between tissue oxygenation and T_2* by examining relative changes in pO_2 and T_2* during standardized (patho)physiologically relevant interventions that modulate renal hemodynamics and oxygenation.

Materials and Methods: ***Animal Model:*** Experiments were performed on 15 male Wistar rats (age 3-4 months, 300-350g). Animals were anesthetized using Urethane (20%; 6 ml/kg BM i.p.). Body temperature was maintained at 37 °C by means of a water-heated warming mat. ***Surgical Preparation:*** A perivascular flow probe was placed around the renal artery from caudal (Fig.1). Fiber optic pO_2/flux probes were placed in the cortex and medulla (Fig.1). For reasons of stability, the cortical probe's tip was advanced from the caudal extremity all the way to the cortical layer of the cranial extremity (Fig.1). Blood pressure was monitored via a femoral artery catheter. ***MR imaging:*** Images were acquired on a 9.4T MR scanner (Bruker Biospec, Germany) using a four-element RX surface coil array and a TX volume coil (d=72mm). T_2* mapping was performed with multi-echo gradient echo imaging (TR=50ms, TE=(1.43-20.69)ms, TA=1:20min). Renal T_2* was monitored for a coronal oblique slice (FOV=(38.2x50.3)mm^2, in plane resolution (230x230)μm^2, slice thickness 1.4mm) placed across the kidney so that the cortical and medullary pO_2 and flux probes were located within the imaging plane as illustrated in Figure 1. ***Experimental protocol:*** Renal T_2* maps were acquired every 3 minutes. Simultaneously, arterial blood pressure, renal blood flow, tissue pO_2 and flux were recorded continuously. Three short-term reversible interventions were performed inside the MR scanner to modulate renal blood oxygenation: aortic occlusion, hypoxia and hyperoxia. The aorta was occluded by inflating a remotely controlled suprarenal aortic occluder. Short periods of hypoxia and hyperoxia were induced by changing the gas flow through a respiratory mask such that the inspiration fraction of oxygen was decreased/increased to 8%/100%.

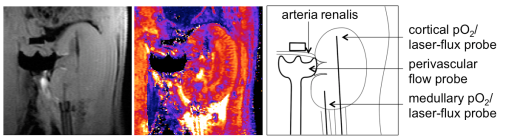

Figure 1: Coronal GRE MR image (TE=1.43ms) of a rat kidney (left) with the corresponding T_2* map (center) and a schematic (right) that illustrates the position of the perivascular flow probe and the cortical and medullary Laser-flux/pO_2 probes. Both invasive probes were located within the imaging plane (visible in the above T_2* weighted image and T_2* map).

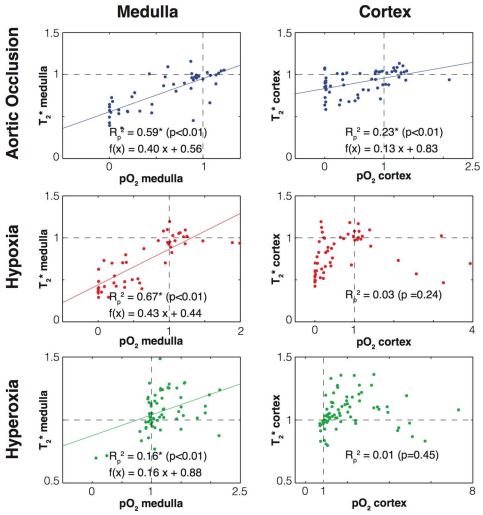

Figure 2: Parametric correlation analysis (Pearson) between relative changes of medullary (left) and cortical (right) T_2* and relative changes of pO_2 for aortic occlusion/recovery (top), hypoxia/recovery (center) and hyperoxia/recovery (bottom). A linear regression curve and respective equation are shown only for significant correlations with * p<0.01.

Results: Pearson's analysis revealed significant linear correlations between relative changes in medullary T_2* and medullary tissue pO_2 for all interventions as highlighted in Figure 2. Differences in the degree of the medullary T_2*/pO_2 correlation were observed for the three brief interventions. The closest correlation was found during hypoxia-recovery. A modest correlation was obtained during occlusion-recovery while hyperoxia-recovery revealed the weakest medullary T_2*/pO_2 correlation. Changes in cortical T_2* and pO_2 yielded a significant linear correlation for aortic occlusion-recovery only.

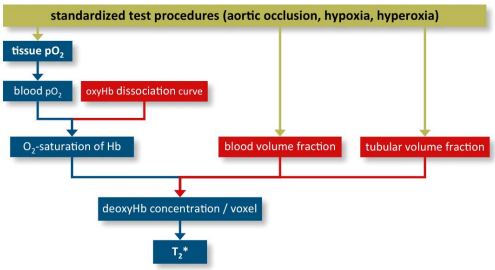

Figure 3: Basic scheme of physiological parameters that affect the relation between tissue pO_2 and T_2*. This includes contributions of the renal blood volume fraction and the tubular volume fraction.

Discussion and Conclusions: Our results demonstrate that MR-PHYSIOL is instrumental to detail the link between renal tissue pO_2 and T_2* *in vivo*. The differences in the T_2*/pO_2 relation obtained for cortex and medulla can be attributed to the vascular volume fraction, which is lower for the inner medulla versus cortex under baseline conditions. Hence passive distension or active vasomotion induced alterations in vascular volume are expected to have a greater effect on the amount of deoxyHb per tissue volume and on T_2* in the cortex than in the medulla. The weak T_2*/pO_2 correlation during hyperoxia-recovery is plausible since almost all of the available Hb in arterial blood is saturated with O_2 under normoxic conditions already. Hyperoxia results in a substantial increase in arterial blood pO_2 but only a minor increase in O_2 saturation of Hb. During hypoxia, on the other hand, oxyHb will significantly drop almost in parallel with blood pO_2 (relation is determined by the oxyHb dissociation curve) such that the correlation of pO_2 to T_2* must be closer than during hyperoxia. Renal tissue pO_2/T_2* correlations were weaker for occlusion-recovery versus hypoxia-recovery, which can be related to a rapid and pronounced decrease in the vascular volume fraction with the onset of occlusion (no inflow of blood via the renal artery, but on-going outflow via the renal vein into the vena cava), which per se would increase T_2*. Consequently, the drop in pO_2 is much faster and more pronounced than that in T_2*. The tubular fraction decreases during occlusion, mostly in favor of the interstitial fraction, which increases due to tubular fluid reabsorption under conditions of arrested blood flow. During hypoxia, tubular fraction decreases due to reabsorption and maintained tubular (out)flow toward the renal pelvis, whereas interstitial fraction will probably not increase because of the maintained peritubular capillary flow that drains the interstitial fluid. To generalize, our results demonstrate that blood volume fraction and tubular volume fraction need to be considered as key physiological parameters that govern the renal T_2* as outlined in Fig.3. To conclude, an unambiguous characterization of renal hemodynamics and oxygenation requires further MR readouts including relative blood volume (RBV) and intravoxel incoherent motion (IVIM) techniques to probe for blood volume fraction and tubular volume fraction.

References: [1] Flemming, J Am Soc Nephrol 2000, [2] Seeliger, J Am Soc Nephrol 2007, [3] Evans, Am J Physiol 2011, [4] Evans, CEPP 2013, [5] Evans, CEPP 2008, [6] Evans, Kidney Int, [7] Evans, Am J Physiol 2008, [8] Pohlmann, Acta Physiol 2013.