Combination of Non-Invasive parametric MRI and Invasive Physiological Measurements: Towards a Hybrid and Integrated Approach for Investigation of Acute Kidney Injury

Jan Hentschel[1], Kathleen Cantow[2], Andreas Pohlmann[1], Karen Arakelyan[1,2], Bert Flemming[2], Mechthild Ladwig[2], Erdmann Seeliger[2], Uwe Hoff[3], Pontus B. Persson[2], and Thoralf Niendorf[1,4]

[1]Berlin Ultrahigh Field Facility (B.U.F.F.), Max Delbrueck Center for Molecular Medicine, Berlin, Germany, [2]Institut für Vegetative Physiologie, Charité Campus Mitte, Berlin, Germany, [3]Nephrology and Intensive Care Medicine, Charité – Universitätsmedizin Berlin, Campus Virchow- Klinikum, Berlin, Germany, [4]Experimental and Clinical Research Center a joint cooperation between the Charité Medical Faculty, and the Max-Delbrueck Center for Molecular Medicine, Berlin, Germany

Introduction: Acute kidney injuries (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 [1,2]. Invasive but quantitative physiological methods are used for targeted probing of kidney hemodynamics and oxygenation in animals *in vivo* through the assessment of kidney perfusion as well as regional perfusion and oxygenation [3]. A very limited number of studies attempted to draw the link between established invasive methods and functional renal MRI in order to explore the applicability of MRI for the detection of changes in renal perfusion and oxygenation [4,5]. Notwithstanding its success these comparisons primarily relied on comparing independent cohorts of animals, which underwent either invasive physiological measurements or MRI. Moreover, the validity of quantitative MRI data as a surrogate marker for renal tissue perfusion and oxygenation has not been systematically examined yet. For all these reasons we set out to combine invasive techniques and non-invasive MRI in an integrated hybrid setup with the ultimate goal to calibrate, monitor and interpret parametric MR and physiological parameters by means of standardized interventions. Here we present a first report on the current status of this integrated multi-modality approach. The feasibility of the combined approach was assessed using stimuli that affect renal hemodynamics and oxygenation, i.e., hypoxia and hyperoxia.

Materials and Methods: ***Animal Model*** Experiments were performed on male, 3-4 months old, Wistar rats with a body mass (BM) of 300-350 g. 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. ***MR Compatibility*** To make the probes used for invasive measurements MR compatible, the metal reflector of an ultra-sound transit-time-difference-based perivascular flow probe (Transonic Systems Inc., Ithaca, USA) was replaced by a ceramic reflector. Two fiber optic probes (Oxford Optronics Ltd, Oxford, UK) capable of measuring tissue pO_2 and flux (mean velocity of erythrocytes) did not require modification. T_2* mapping of these probes in agarose/tissue showed only minor susceptibility effects in close proximity to the probe that did not interfere with the parametric MRI of the kidney. ***Surgical Preparation*** Conventional methods for insertion and fixation of invasive probes were adapted to the spatial constraints of the MR scanner. The Transonic flow probe was placed around the renal artery from caudal (Fig.1, top). Gauze around the cabling was fixed with sutures to retroperitoneal muscles. The fiber optic pO_2/ flux probes were placed in the cortex and medulla (Fig.1, top). Space limitations required ventrocaudal insertion of both probes. Silicone tubes surrounding the fibers were armed with gauze that was fastened to the kidney's surface by means of histoacryl glue to prevent probe dislocation. For reasons of stability, the cortical probe's tip was advanced from the caudal extremity centrally through the kidney all the way to the cortical layer of the cranial extremity. Blood pressure was monitored via a catheter placed in the femoral artery and a pressure transducer (Viggo-Spectramed, Swindon, UK). To avoid displacement of the probes and to face the spatial constraints of the MR scanner bore, a dedicated animal holder (Fig.1, bottom) was built using 3D printing (BST 1200es, Alphacam GmbH, Schorndorf, Germany). ***MR Imaging*** Images were acquired on a 9.4T MR scanner (Bruker Biospec, Ettlingen, Germany) using a four-element RX surface coil array and a TX volume coil (dia=72mm). T_2 mapping: MSME, TR=550ms, TE=10-70ms (7 values), TA=1:40min. T_2* mapping: MGE, TR=50ms, TE=1.43-20.69ms (10 values), TA=1:20min. Renal T_2/T_2* were monitored for a coronal oblique slice (FOV=(38.2x50.3) mm^2, matrix 169x215, in plane resolution (230x230)μm^2, slice thickness 1.4-1.5mm). ***Experimental Protocol*** T_2* and T_2 maps were acquired interleaved. Simultaneously, arterial blood pressure, renal blood flow, tissue pO_2 and flux were logged continuously using a sampling rate of 1Hz. Feasibility tests included two stimuli: hypoxia (10% oxygen, 90% nitrogen) and hyperoxia (100% oxygen). During baseline (~15min) and post stimulus recovery (~15min) room air was provided (normoxia).

Results: Fig. 2 shows exemplary results obtained from simultaneous invasive measurements and parametric MRI for the two stimuli. For all physiological probes, measurements free of artifacts were obtained in between the MR scans, which demonstrates MR compatibility. At onset of hypoxia, both, tissue pO_2 and T_2* decreased substantially. Erythrocyte flux increased in response to hypoxia. During hyperoxia, pO_2, T_2* and renal blood flow increased simultaneously. All parameters returned to baseline within 15 minutes of recovery. Both interventions led to a rather uniform T_2*/T_2 decrease/increase across the kidney. A closer examination of the flux signal trace in the hypoxia experiment revealed signal elevations that correlated with the start and duration of the MR scans. This signal distortion can be attributed to an interference with the MR measurement and might be caused by vibrations related to the fast switching scheme of MR gradients. The pO_2 probes show small peaks that correlate with the beginning of each MR scan.

Discussion and Conclusions: Our preliminary results demonstrate that simultaneous measurement of tissue pO_2, flux, renal blood flow, arterial blood pressure and MRI is feasible. Notwithstanding this success at this stage of the development process the simultaneous acquisition of MR data and invasively obtained physiological data presents some remaining challenges because of interference of the probes with electro-magnetic fields. Hence we will drive further explorations into the root cause of the interferences with the goal to substantially reduce if not eliminate distortions of the physiological signal traces. To approach this goal we will make use of the physiological signal traces obtained during silent MR periods which were found to be immune to interference with the main magnetic field. With these results in mind we will enter into further *in vivo* experiments to perfect the proposed hybrid setup and to refine the surgical and experimental procedures. To conclude, the proposed hybrid approach allows tracking and comparison of invasive physiological parameters with parametric MRI in the same animal. The proposed hybrid approach eliminates the need for different cohorts of animals to compare physiological data with MRI. It enables calibration, monitoring and benchmarking of parametric MRI results versus physiological measurements. The hybrid approach holds the promise to shed more light onto the (patho)physiological processes behind the development of acute kidney injury.

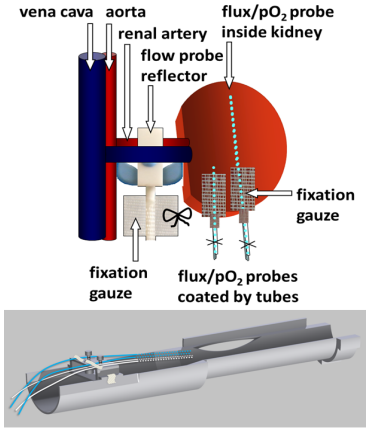

Figure 1: top) Basic scheme of the setup highlighting the implantation of the perivascular flow probe and the cortical and medullary pO_2/flux probe. **bottom)** Basic scheme of the custom made animal holder with a hight-adjustable bridge to fix the cabling used for the invasive probes.

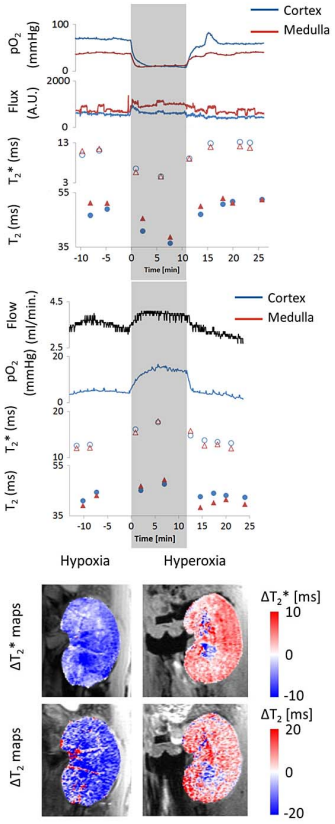

Figure 2: Simultaneous tracking of renal blood flow, cortical and medullary pO_2, flux and T_2*/T_2 in the MR scanner for 2 interventions: **top)** hypoxia (n=1) and **middle)** hyperoxia (n=1). The interventions start at t = 0 min and the duration is indicated by the gray shading. **Bottom)** T_2*/T_2 difference map (color-coded, overlay on anatomical MR image) between last point of intervention and baseline.

References: [1] Eppstein, N Engl J Med 1995, [2] Seeliger, J Am Soc Nephrol 2007, [3] Flemming, J Am Soc Nephrol 2000, [4] Li, Inv Rad 2009, [5] dos Santos, Inv Rad 2007

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