

Ferumoxyl Enhanced Steady-State MRI Reveals Renal Blood Volume Decrease During Aortic Occlusion

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Target audience: MR scientists, clinicians and clinical scientists with an interest in acute kidney injury.

Introduction and Purpose: Acute kidney injuries (AKI) of various origins share one common feature in the initiating chain of events: imbalance between local tissue oxygen delivery and oxygen demand.^{1,2} Quantitative parametric MRI (T_2^* mapping) offers a non-invasive approach to probe renal oxygenation but provides a surrogate rather than a quantitative measure of oxygen saturation. Although renal T_2^* reflects blood oxygenation rather than renal tissue oxygenation, changes in tissue pO_2 and T_2^* may be closely related. However, their link is influenced by effects including diffusional O_2 shunting and plasma skimming.³ Previously we reported changes in renal T_2^* induced by aortic occlusion vs hypoxia and renal arterio-venous occlusion vs hypoxia.^{4,5} A closer examination revealed that T_2^* alterations of renal arterio-venous occlusion were more pronounced than those induced by hypoxia, yet arterial (aortic) occlusion induced a smaller T_2^* effect versus hypoxia. This observation might be explained by variations in renal blood volume (RBV) and suggests that blood volume fraction and tubular volume fraction need to be considered as key physiological parameters that influence renal T_2^* . We hypothesized that monitoring of RBV using an intravascular contrast agent could provide evidence for a significant reduction in RBV during aortic occlusion, and hence for the relevance of RBV in the interpretation of renal T_2^* . To test our hypothesis we established RBV estimation with the novel intravascular USPIO ferumoxyl at 9.4 Tesla in rats and compared the effects of renal arterio-venous occlusion (AVO) with suprarenal aortic occlusion (AO) while monitoring renal T_2^* .

Methods: Animal model: 4 female Sprague-Dawley rats (aged 2 months, 240–260g) underwent experiments inside a 9.4T MR system (Bruker Biospin, Germany).⁵ The rats were anesthetized using urethane (20% in water, 6 ml/kg body mass) and kept at a constant core body temperature of 37°C during surgery and MRI. For arterial or arterio-venous occlusion a remotely controllable hydraulic occluder was placed either around the suprarenal aorta (n=2)⁴ or around the renal artery and vein (n=2)⁵ respectively. Following transferal of the rat into the MR scanner T_2^* was monitored with a temporal resolution of ~3 minutes. A short-term reversible ischemia was induced by closing the remotely controlled hydraulic occluder for 3 minutes, followed by a reperfusion phase of ~15 minutes. Subsequently an intravascular iron oxide (ferumoxyl) was injected i.v. at a dose of 6 mg Fe/kg and after a mixing time of 2 minutes the short-term reversible ischemia was repeated. Right after onset of each occlusion the interruption of renal blood flow was confirmed by time-of-flight MR angiography of the kidney. **MR imaging:** Experiments were carried out using a birdcage RF resonator (TX) in conjunction with a four channel RF coil array (RX; Bruker Biospin, Germany) customized for rats. Local B_0 shimming on a voxel tailored to the kidney was performed first. Parametric T_2^* mapping used a respiratory gated multi gradient echo (MGE) sequence (TR = 50 ms, number of echoes = 10, first TE = 1.43 ms, echo spacing = 2.14 ms, averages = 4) with a total acquisition time of approx. 1 min 20 s. A coronal oblique image slice was acquired with a spatial in plane resolution of (226x445) μm^2 and a slice thickness of 1.4 mm.

Results: Fig.1 shows T_2^* -weighted images at baseline, during renal arterio-venous occlusion (AVO) and during aortic occlusion (AO). During AVO cortical and medullary signal intensity decreased. In contrast, during AO an increase in signal intensity in the renal cortex was observed, particularly after CA administration. Quantitative changes in renal T_2^* are demonstrated in Fig. 2. In naïve kidneys renal T_2^* decreased by 37-57% during AVO but changed by only a few percent during AO (Fig.2). Outer medullary (OM) and cortical (COR) T_2^* displayed different behaviors: though changes were small, OM T_2^* decreased, while COR T_2^* increased. Post contrast agent T_2^* still decreased by 28-49% during AVO but increased by 7-14% during AO (Fig.2). The latter indicates a large outflow of iron labeled blood.

Discussion and Conclusion: Our results demonstrated that effects of AVO and AO on renal T_2^* are rather different. Assuming the net out/in-flow of blood during AVO being negligible, the observed strong T_2^* decrease is consistent with the expected rise in deoxyHb concentration. Unlike AVO, AO may allow for a significant outflow of blood, which – with regards to the local deoxyHb amount per image voxel – counteracts the deoxygenation of the renal blood. The oxygenation induced T_2^* decrease is reduced, or even reversed, by a RBV decrease. Following i.v. administration of additional iron oxide in the form of USPIOs, the balance of the two competing T_2^* effects (increase in deoxyHb vs decrease in RBV) is shifted in favor of sensitivity to RBV changes. Consequently, the decrease in RBV now prevailed over the deoxyHb rise and T_2^* increased in both, renal cortex and outer medulla. The smaller AVO effect post-CA might be due to the nonlinearity of T_2^* vs iron concentration. In conclusion, our results demonstrate that RBV decreases during suprarenal aortic occlusion. Hence, *in-vivo* the blood volume fraction may vary considerably so that an unambiguous characterization of renal oxygenation by T_2^* requires further MR readouts such as renal blood volume (RBV). These efforts should be paralleled by invasive but quantitative physiological measurements using MR-PHYSIOL⁶ to gain a better insight into renal oxygenation and hemodynamics.

References: [1] Seeliger, J Am Soc Nephrol 2007, 18(11):2912, [2] Evans, Am J Physiol 2011, 300(4):R931, [3] Evans, CEPP 2008, 35(12):1405, [4] Arakelyan, Acta Physiol, 2013, 208(2): 202, [5] Pohlmann, PLoS ONE, 2013, 8(2):e57411, [6] Pohlmann, Acta Physiol, 2013, 207(4):673.

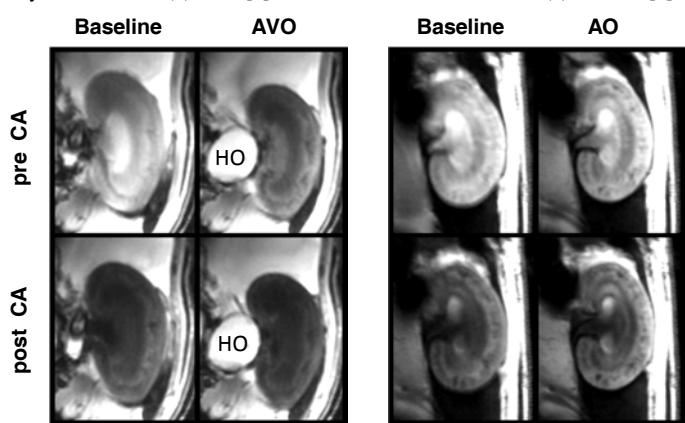


Figure 1: T_2^* -weighted images (average of all echoes) at baseline, during renal arterio-venous occlusion (AVO) and during suprarenal aortic occlusion (AO). Images before contrast agent (CA; top row) are compared with images after contrast agent (bottom row). During AVO cortical and medullary signal intensity decreased. In contrast, during AO an increase in signal intensity in the renal cortex was observed, particularly after CA administration. The inflated hydraulic occluder (HO) is visible during AVO.

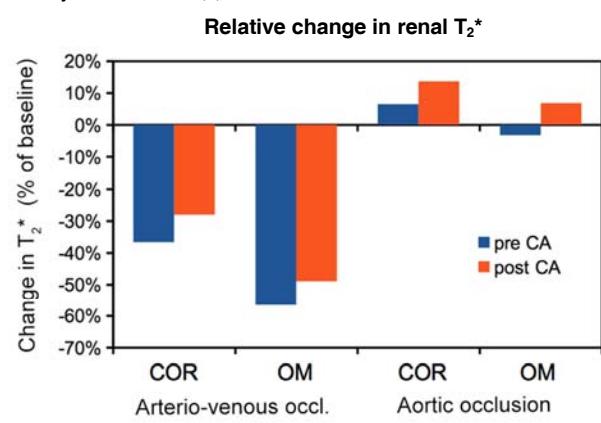


Figure 2: Relative change in renal T_2^* during renal arterio-venous occlusion (AVO) and aortic occlusion (AO) compared to baseline. Medians for the cortex (COR) and outer medulla (OM) are shown pre and post contrast agent administration. In the naïve kidney renal T_2^* decreased by 37-57% during AVO but changed by only a few percent during AO. Post contrast agent T_2^* still decreased by 28-49% during AVO but now increased by 7-14% during AO, indicating a large outflow of iron labeled (USPIO and deoxyHb) blood.