Ferumoxytol Enhanced T_2* Mapping for Combined Renal Oxygenation and Blood Volume Assessment at 9.4T

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Target audience: MR scientists, clinicians and clinical scientists with an interest in characterization of renal oxygenation and blood volume.

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. Changes in tissue pO_2 and T_2* may be closely related, but their link is influenced by various effects, including changes in vascular volume fraction. Previously we reported T_2* alterations of renal arterio-venous occlusion were more pronounced than those induced by hypoxia, while arterial occlusion induced a smaller T_2* effect than hypoxia.[4,5] This observation might be explained by variations in renal blood volume (RBV) and suggests that blood volume fraction should be considered a key physiological parameter that influences renal T_2*. We hypothesized that administration of the intravascular contrast agent (CA) ferumoxytol permits *in vivo* RBV assessment, which under some physiological conditions may be essential for the unambiguous interpretation of renal T_2*. Yet, a ferumoxytol dose tailored for RBV monitoring at 9.4T remains to be established. The need for a high CA dose that enhances RBV sensitivity competes with the need for a relatively low CA dose to permit a sufficient signal-to-noise-ratio (SNR) and to avoid baseline T_2*-shortening impairing sensitive detection of stimulus effects. To determine a suitable ferumoxytol dose we propose combining simulation based error estimation with *in vivo* T_2* and SNR data for staggered CA doses at baseline and during a physiological stimulus of interest. For this purpose we monitored renal T_2* during baseline conditions and short periods of venous occlusion at iron doses ranging from 0 to 10 mg Fe/kg. Choice of ferumoxytol dose was based on the relation of the noise induced T_2* error to the occlusion induced T_2* change.

Methods: ***Animal model:*** male Wistar rats (aged 2 months, 288–330g) were anesthetized (20% urethane in water, 6 ml/kg) and kept at a constant core body temperature of 37°C during surgery and MRI.[5] For venous occlusion a remotely controllable hydraulic occluder was placed around the renal vein. Following transferal of the rat to the MR scanner T_2* was monitored using the protocol described below. A short-term reversible ischemia was induced by closing the hydraulic occluder for 3 minutes, followed by a reperfusion phase of ~20 minutes. Venous occlusion was confirmed by time-of-flight MR angiography of the kidney. Subsequently ferumoxytol was injected i.v. at a dose of 2 mg Fe/kg and after a mixing time of 2 minutes the short-term reversible venous occlusion was repeated. This procedure was reiterated for cumulative doses of 4,6,8, and 10 mg Fe/kg. ***MR imaging:*** *in vivo* MRI was performed using a 9.4 T animal scanner (Bruker, Ettlingen, Germany) in conjunction with birdcage RF resonator and a four channel receive RF coil array (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 respiratory gated multi gradient echo (MGE) imaging (TR = 50 ms, echoes = 10, first TE = 1.43 ms, echo spacing = 2.14 ms, averages = 4)[5]. A coronal oblique slice across the kidney was acquired with a spatial in plane resolution of (226x445) μm^2 and a slice thickness of 1.4 mm. ***Dose finding:*** T_2* mapping was performed for the *in vivo* data, as well as for *synthetic* data consisting of perfect exponential T_2* decays with added Gaussian noise. For various combinations of true T_2* (1 to 50ms) and SNR (10 to 1000) T_2* was fitted to 10000 noisy synthetic data sets and the mean T_2* error was calculated. Confidence intervals (5-95%) of *in vivo* renal T_2* and SNR were obtained from histogram analysis. Using semi-automatically placed regions-of-interest[5] we calculated cortical and medullary changes in T_2* induced by ferumoxytol injection and venous occlusion. Finally, we estimated the error for the observed venous occlusion effect on T_2*, by performing the T_2*-mapping simulations with the actual *in vivo* renal T_2* and SNR. Errors in T_2* at baseline and occlusion were combined into a total ΔT_2* error using error propagation: $\delta\Delta T_2^* = \sqrt{(\delta T_2^*_{baseline})^2 + (\delta T_2^*_{occlusion})^2}$. The relative error in percent of the effect (here the occlusion effect) was expressed as $\delta\Delta T_2^* / \Delta T_2^* \cdot 100$.

Results: Ferumoxytol administrations decreased cortical and medullary intensity in renal T_2*-weighted images (Fig.1). The effect of venous occlusion was substantial at all ferumoxytol doses. The error matrix shown in Fig.2. reveals that the T_2*-mapping error is below 1 ms for almost all *in vivo* baseline conditions at iron doses 0-10 mg Fe/kg (dashed ROIs). Cortical and outer medullary T_2* effects of ferumoxytol injection strongly increase with iron dose, while the T_2* effect of venous occlusion rapidly decreases with iron dose (Fig.3). For dose finding the relative error of the venous occlusion T_2* effect was assessed (Fig.4). This error is pronounced with increasing iron dose and exceeds 10% for doses greater than 4 mg Fe/kg.

Discussion and Conclusion: Our results demonstrate that iron doses up to at least 10 mg Fe/kg are suitable for a ferumoxytol enhanced steady state RBV assessment. Detecting of stimulus induced T_2* variations (RBV and/or oxygenation) becomes less sensitive with increasing ferumoxytol dose. Dose finding for measuring venous occlusion induced T_2* changes with our 9.4T protocol and a maximum acceptable error of approx. 10% yielded a dose of 4 mg Fe/kg. The contrast mechanism of ferumoxytol is a reduction of T_2*, which is similar to the mechanism of the BOLD effect that results from variations in deoxyHb concentration per tissue volume. This represents a challenge as well as an opportunity, because it potentially permits the combined assessment of renal oxygenation and blood volume, but requires several measurements of T_2* under different conditions in order to unravel the contributions of $\Delta T_2^*_{RBV}$ and $\Delta T_2^*_{BOLD}$. Renal blood volume fraction may vary considerably, e.g. due to changes in renal perfusion pressure, vasoconstriction/-dilation or tubular distension. Changes in renal oxygenation are likely to be accompanied by changes in vascular volume fraction, in part owed to the autoregulation of the kidney. Unambiguous characterization of renal oxygenation by T_2* hence requires further MR readouts such as renal blood volume. Combining T_2*-mapping with ferumoxytol, paralleled by calibration via invasive but quantitative physiological measurements using MR-PHYSIOL[6] might help to gain a better insight into renal oxygenation and hemodynamics.

References: [1] Seeliger, Europ Heart J 2012, 33:2007, [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.

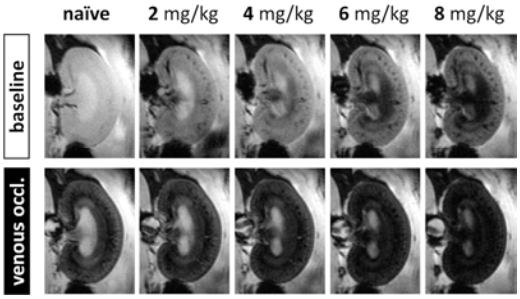

Figure 1: Effect of venous occlusion on T_2*-weighted images. Renal T_2*-weighted images (TE=3.57ms) during baseline (top) and venous occlusion (bottom) at ferumoxytol doses of 0,2,4,6 and 8 mg Fe/kg.

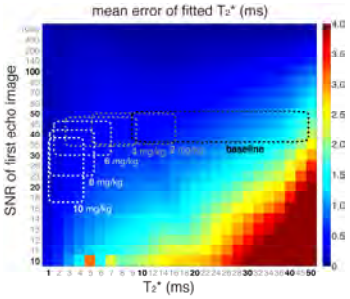

Figure 2: Estimated error of T_2*-mapping. Dependency of absolute error in T_2* (from simulations) on SNR and true T_2*. ROIs indicate ranges of renal SNR and T_2* measured *in vivo*.

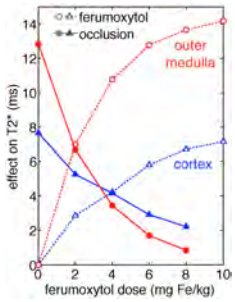

Figure 3: T_2* effects of ferumoxytol injection and venous occlusion. Absolute change in renal cortical and outer medullary T_2*.

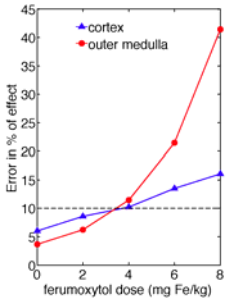

Figure 4: Dose finding. Relative error of venous occlusion T_2* effect. Error (derived from simulations) vs measured T_2* change.