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How Bold is Blood Oxygenation Level Dependent (BOLD)

Magnetic Resonance Imaging of the Kidney?

Opportunities, Challenges and Future Directions

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Abstract

Renal tissue hypoperfusion and hypoxia are key elements in the pathophysiology of acute kidney injury and its progression to chronic kidney disease. Yet, *in vivo* assessment of renal haemodynamics and tissue oxygenation remains a challenge. Many of the established approaches are invasive, hence not applicable in humans. Blood oxygenation level dependent (BOLD) magnetic resonance imaging (MRI) offers an alternative. BOLD-MRI is non-invasive and indicative of renal tissue oxygenation. Nonetheless recent (pre-)clinical studies revived the question as to how bold renal BOLD-MRI really is. This review aims to deliver some answers. It is designed to inspire the renal physiology, nephrology, and imaging communities to foster explorations into the assessment of renal oxygenation and haemodynamics by exploiting the powers of MRI. For this purpose the specifics of renal oxygenation and perfusion are outlined. The fundamentals of BOLD-MRI are summarized. The link between tissue oxygenation and the oxygenation sensitive MR biomarker T_2^* is outlined. The merits and limitations of renal BOLD-MRI in animal and human studies are surveyed together with their clinical implications. Explorations into detailing the relation between renal T_2^* and renal tissue partial pressure of oxygen (pO_2) are discussed with a focus on factors confounding the T_2^* versus tissue pO_2 relation. Multi-modality *in vivo* approaches suitable for detailing the role of the confounding factors that govern T_2^* are considered. A schematic approach describing the link between renal perfusion, oxygenation, tissue compartments and renal T_2^* is proposed. Future directions of MRI assessment of renal oxygenation and perfusion are explored.

Introduction

Kidney diseases are a global health burden with steadily increasing incidence (Eckardt et al., 2013, Lameire et al., 2013, Leung et al., 2013). Two million per year is the estimated worldwide death toll of acute kidney injury (AKI) (Thakar et al., 2009, Thakar, 2013, Ali et al., 2007). Renal tissue hypoperfusion and hypoxia are considered to be key elements in the pathophysiology of AKI and the progression from acute kidney injury to chronic kidney diseases (CKD) (Persson, 2013a, Singh et al., 2013, Evans et al., 2008b, Evans et al., 2011a, Evans et al., 2013, Chawla and Kimmel, 2012, Seeliger et al., 2012, Legrand et al., 2008). Disturbance of the balance between renal oxygen supply and demand is also suggested to play a major role in the pathophysiology of diabetic nephropathy (Friederich-Persson et al., 2013, Hansell et al., 2013). Admittedly, it is too early to make ultimate statements on the role of renal hypoperfusion and hypoxia in these renal disorders since *in vivo* assessment of renal haemodynamics and oxygenation constitutes a challenge. All modalities available in current experimental and translational research practice have inherent limitations and methodological shortcomings (Evans et al., 2008b, Prasad, 2006b, Evans et al., 2007, Pohlmann et al., 2013a). Many of the established approaches are invasive, hence applicable in animal studies but not in humans. On the clinical side, prevention and therapy of AKI and CKD largely rely on empirical knowledge. With an increasing incidence of AKI in all acute care hospitalizations, risk assessment strategies and therapeutic options are limited (Thakar et al., 2009, Thakar, 2013, Hoste and Schurgers, 2008, Ali et al., 2007, Chertow et al., 2005). Translational approaches - although urgently warranted - are still scarce (Zarjou et al., 2012, Evans et al., 2013). The magnitude of unsolved problems and clinical needs motivated a recent quest for putting extra weight behind explorations into haemodynamic influences on kidney oxygenation to enhance the understanding of renal diseases that are induced or promoted by renal tissue hypoperfusion and hypoxia (Evans et al., 2013). The impact of changes in renal haemodynamics on tissue oxygenation, by virtue of the complexity of renal

(patho)physiology, cannot necessarily be predicted intuitively. It requires a comprehensive approach using multi-faceted measuring modalities including non-invasive imaging such as ultrasound, computer tomography and magnetic resonance imaging (Brabrand et al., 2014, Damkjaer et al., 2012, Pohlmann et al., 2013a) that may be supported by insights from simulations modeling renal tissue (Evans et al., 2013, Zhang et al., 2014).

Magnetic resonance imaging (MRI) offers a non-invasive technique to obtain insight into renal perfusion and oxygenation under (patho)physiological conditions (Zhang et al., 2013). MRI affords full kidney coverage, soft tissue contrast that helps to differentiate the renal layers, seconds to minutes temporal resolution, support of longitudinal studies and high anatomic detail (Prasad and Epstein, 1999, Prasad et al., 2001, Prasad, 2006b, Li et al., 2008, Haque et al., 2011, Michaely et al., 2012, Arakelyan et al., 2013b, Pohlmann et al., 2013a, Pohlmann et al., 2013b, Hueper et al., 2013). Blood oxygenation level dependent (BOLD) MRI is thought - if not touted - to provide a surrogate of renal tissue oxygenation (Prasad and Epstein, 1999, Prasad et al., 2001, Prasad, 2006b, Li et al., 2008, Haque et al., 2011, Peng et al., 2013, Morrell et al., 2013, Menzies et al., 2013, Pruijm et al., 2013a, Pruijm et al., 2013b, Pruijm et al., 2013c, Liss et al., 2013, Gloviczki et al., 2011, Rognant et al., 2012, Park et al., 2012, Donati et al., 2012, Ebrahimi et al., 2012, Chrysochou et al., 2012, Rognant et al., 2011, Warner et al., 2011, Gloviczki et al., 2009, Rossi et al., 2013). Renal BOLD-MRI methodology has matured and a broad range of preclinical and clinical applications have been reported. The eye-opening quality of the anatomical and functional images of the kidney created excitement among the diagnostic imaging community and is the driving force for broader clinical studies. The clinical implications feed into a broad spectrum of physiology, nephrology, radiology and other related fields of basic science and clinical research. The ever growing number of pioneering reports eloquently referring to renal BOLD-MRI is an inherent testament to the value of non-invasive MRI to renal (patho)physiology. This progress creates the temptation to sing the praises of renal BOLD-MRI. Yet recent findings and considerations

derived from renal BOLD-MRI in preclinical and human studies revitalized and nurtured the reflective and intense debate on “how bold is BOLD-MRI of the kidney?” (Mason, 2006, Evans et al., 2007, Michaely et al., 2012, Neugarten, 2012, Pohlmann et al., 2013a, Arakelyan et al., 2013, Pohlmann et al., 2014a).

Realizing the progress, opportunities, challenges and caveats of renal BOLD-MRI this review is not a literature survey but an attempt to inspire the renal physiology, nephrology, biomedical and diagnostic imaging communities to foster explorations into the remaining unresolved questions and technical obstacles behind non-invasive assessment of renal oxygenation and haemodynamics. To meet this goal, this review first outlines the specifics of renal oxygenation and perfusion. Then the basic physical and biophysical principles of BOLD-MRI are described. This includes the link between tissue oxygenation and the MR based biomarker T_2^* , which provides a surrogate for blood oxygenation. Early and frontier applications of renal BOLD-MRI in small animal and human studies are explored together with their clinical implications. Recent explorations into detailing the relation between renal T_2^* and renal tissue partial pressure of oxygen (pO_2) are discussed. Experimental results that underscore the factors confounding the $T_2^*/\text{tissue } pO_2$ relation are surveyed. Multi-modality *in vivo* approaches for probing renal perfusion and oxygenation including parametric MRI, quantitative physiological measurements and optical imaging techniques are considered. An empirical approach that describes the link between renal perfusion, renal oxygenation, tissue compartments and renal T_2^* is proposed. A concluding section ventures a glance beyond the horizon and explores future directions of MRI based assessment of renal oxygenation and perfusion.

All the animal experiments performed by the authors and shown in the figures were carried out in accordance with published guidelines (Persson, 2013b).

Unique aspects of renal haemodynamics and oxygenation

Renal oxygenation constitutes a delicate balance between oxygen delivery, as determined by renal blood flow and arterial O₂ content, and O₂ consumption, for which energy-dependent tubular reabsorption is the major determinant. Increased renal blood flow (RBF) is, in general, accompanied by increased glomerular filtration rate (GFR), and therefore necessitates increased tubular reabsorption (Blantz and Deng, 2007, O'Connor, 2006, Rosen et al., 1992, Evans et al., 2008b, Evans et al., 2013). As compared to most non-renal tissue, whole-kidney blood flow is high and whole-kidney arterio-venous difference in O₂ content is small. Yet renal tissue perfusion and oxygenation is highly heterogeneous. Virtually all of the blood flowing into the kidney perfuses the cortex. The medulla is perfused by a small fraction (about 10% of total RBF) of blood that had traversed the cortex. Even intra-layer perfusion is quite heterogeneous. In accordance, tissue pO₂ is low in the medulla and also varies within the respective layer (Edwards et al., 2000, O'Connor et al., 2006b, Evans et al., 2008a, Lubbers and Baumgartl, 1997, Evans et al., 2013). Three additional mechanisms substantially contribute to low renal tissue pO₂. (i) The particular architecture of the intra-renal vasculature enables shunt diffusion of O₂ from arteries to veins in the cortex as well as from descending to ascending vasa recta in the medulla. (ii) The vascular architecture also promotes differential distribution of erythrocytes and plasma at certain vessel branches (plasma skimming), which results in different haematocrit and O₂ content of blood perfusing the daughter vessels. (iii) The Fåhræus-Lindqvist effect lowers the haematocrit in the long and narrow vasa recta supplying the medulla, which lowers the O₂ content of blood perfusing the medulla. (Evans et al., 2008a, O'Connor et al., 2006a, Leong et al., 2007, Gardiner et al., 2012, Edwards et al., 2000, Jonsson et al., 1992, Evans et al., 2013). Based upon studies on animal models of x-ray contrast-induced AKI, ischaemia/reperfusion injury, endotoxemic models of sepsis-induced AKI, and of diabetic nephropathy, intra-renal hypoxia is generally deemed a key pathophysiologic event in these disorders (Hoff et al., 2011, Seeliger et al., 2012, Heyman et

al., 2012, Brezis and Rosen, 1995, Evans et al., 2013, Legrand et al., 2008, Bellomo et al., 2012, Singh et al., 2013, Friederich-Persson et al., 2013, Hansell et al., 2013, Abdelkader et al., 2014).

The kidney is equipped with efficient mechanisms of autoregulation, i.e., the ability to maintain RBF and GFR relatively constant in the face of moderate changes in renal perfusion pressure (RPP) (Just, 2007, Seeliger et al., 2009). It has been suggested that autoregulatory mechanisms also serve the purpose of balancing O₂ delivery with O₂ demand that arises from tubular reabsorption. It is conceivable that in the setting of renal disorders autoregulatory mechanisms create a vicious circle in which low perfusion results in tissue hypoxia that in turn further reduces perfusion. (Blantz and Weir, 2004, O'Connor, 2006, Osswald et al., 1996, Seeliger et al., 2009, Evans et al., 2013). The differential perfusion and oxygenation of renal tissue is subject to changes induced by a variety of (patho)physiological factors. Alterations and redistributions of perfusion and/or of pO₂ were reported from animal models emulating various forms of kidney disorders (Seeliger et al., 2007, Olof et al., 1991, Warner et al., 2009, Evans et al., 2011b, Evans et al., 2013, Pohlmann et al., 2013b, Hultstrom, 2013, Ahmeda et al., 2013, Liu et al., 2013).

Blood oxygenation sensitive MRI

BOLD-MRI is susceptible to bulk microscopic magnetic field perturbations around blood vessels which are induced by paramagnetic deoxygenated haemoglobin (Hb) (Ogawa et al., 1990, Ogawa, 2012). These microscopic magnetic field inhomogeneities affect the effective transversal MR relaxation time T₂* (Zhao et al., 2007, Ogawa et al., 1990). T₂* describes the loss of coherence and decay of the MR signal. T₂* is governed by $1/T_2^* = 1/T_2 + 1/T_2'$, with T₂ being the transverse relaxation time and T₂' embodying susceptibility related contributions (Brown et al., 2014). T₂* weighted MRI is sensitive to changes in the amount of deoxygenated Hb (deoxy Hb) per tissue volume element (voxel).

T_2^* decreases and a signal attenuation in T_2^* -weighted MR images occurs if the volume fraction of deoxy Hb increases. Although T_2^* is widely assumed to provide a surrogate of renal tissue oxygenation, variations in T_2^* may only reflect changes in blood oxygenation (Notohamiprodjo et al., 2010). This distinction is of relevance since renal blood oxygenation and renal tissue oxygenation can vary independently due to arterio-venous O_2 -shunting and plasma skimming (Evans et al., 2008b, Evans et al., 2007). Changes in [vessel volume]/[tissue volume] induced by active vasomotion or passive circular vessel distension/compression also alter the amount of deoxy Hb per tissue volume and hence T_2^* (Evans et al., 2008b).

T_2^* sensitization is given by the echo time (TE). TE is defined by the time between MR signal excitation and MR signal readout (Bernstein et al., 2004). TE governs the loss of phase coherence of the MR signal due to spin dephasing (Bernstein et al., 2004). T_2^* sensitized MRI is most sensitive to blood oxygenation changes when TE is equal to T_2^* . Blood oxygenation induced T_2^* changes exhibit a linear relationship with the magnetic field strength (Turner et al., 1993, van der Zwaag et al., 2009, Donahue et al., 2011, Meloni et al., 2013). The most widely used techniques for T_2^* sensitized renal MRI are echo-planar imaging (EPI) and gradient echo imaging (Brown et al., 2014, Bernstein et al., 2004). EPI offers excellent temporal resolution and reasonable spatial resolution. Notwithstanding this capability, EPI is prone to magnetic susceptibility artifacts. These artifacts present themselves as signal loss and image distortion. This effect is severe at high magnetic field strengths, since T_2^* is shortened versus low magnetic fields, and is particularly pronounced in regions with poor main magnetic field homogeneity. This constitutes a challenge for T_2^* sensitized MRI of renal areas adjacent to the intestine or abdominal fat. This challenge shifted the preference to gradient echo imaging. Gradient echo imaging affords an in-plane spatial resolution as good as 50 μm (Xie et al., 2012) in *ex vivo* MR microscopy (Figure 1a) of freshly excised kidneys (Figure 1b) and tissue contrast (Figure 1c) superior to x-ray (Figure 1d). *In vivo* gradient echo imaging of the kidney affords high anatomical detail using an in-plane spatial resolution as

good as about 220 μm (Figure 1e). The heavy T_2^* -weighting required to make gradient echo images sensitive to changes in the blood oxygenation level necessitates a long TE. TE governs the T_2^* contrast between renal layers, i.e., cortex, outer medulla and inner medulla (Figure 1f). Parametric mapping provides quantitative data of the relaxation time T_2^* . It is accomplished by acquiring a set of images each encoded with a different T_2^* weighting. This is achieved by altering TE values. Parametric mapping provides a means for monitoring renal T_2^* rather than tracking signal intensity changes in individual T_2^* weighted images of the kidney. Renal T_2^* mapping is primarily conducted with multi-echo gradient echo techniques, which acquire a train of gradient refocused echoes after the initial excitation, with each echo being independently T_2^* weighted.

Opportunities of T_2^* sensitized MRI for probing renal oxygenation and perfusion

The assumption that T_2^* provides a surrogate of renal tissue oxygenation is based upon the T_2^* dependence on O_2 saturation of Hb (StO_2) and motivated by the link between StO_2 , blood pO_2 , and tissue pO_2 . T_2^* or its reciprocal value ($R_2^*=1/T_2^*$) have been employed in numerous (pre)clinical studies as an MR based marker and surrogate of intra-renal oxygenation. T_2^* -mapping has been deemed ideally suited for probing intra-renal oxygenation (Prasad, 2006a). Renal T_2^* has even been suggested to exhibit a strong correlation with renal tissue pO_2 (Pedersen et al., 2005). Accordingly, T_2^* sensitized MRI was employed in a broad spectrum of experimental research applications. Animal studies utilized T_2^* -based monitoring of renal oxygenation (i) during focal renal ischaemia (Vexler et al., 1993), renal ischaemia/reperfusion (Figure 2) (Oostendorp et al., 2011, Pohlmann et al., 2013b), and chronic renal artery stenosis (Rognant et al., 2011), (ii) following administration of x-ray contrast media (Arakelyan et al., 2013, Li et al., 2014, Zhang et al., 2012b, Haneder et al.,

2012) (Figure 2), (iii) during reversible interventions including hypoxia (Figure 2), hyperoxia (Figure 2), and short-lasting aortic occlusion (Arakelyan et al., 2013), (iv) during acute unilateral ureteral obstruction (Pedersen et al., 2005), (v) following administration of diuretics (Kusakabe et al., 2010), (vi) during water loading (Ji et al., 2010) and (vii) in early stages of experimental diabetes (dos Santos et al., 2007).

Numerous human studies confirmed the potential for clinical application of renal BOLD-MRI. BOLD-MRI has been reported to be efficient for assessment of human renal tissue oxygenation and its alterations induced by various interventions such as breathing of carbogen (95% O₂, 5% CO₂) or pure oxygen (Boss et al., 2009), administration of indomethacin or an x-ray contrast medium (Hofmann et al., 2006), infusion of diuretics (Gloviczki et al., 2010, Zhang et al., 2014, Hall et al., 2014), and acute unilateral ureteral obstruction by kidney stones (Thoeny et al., 2008). In patients with atherosclerotic renal artery stenosis pre and post stent revascularisation and in a control group of patients with essential hypertension BOLD-MRI showed a good relationship with renal perfusion (Saad et al., 2013). BOLD-MRI may also be used to assess the functional status of transplanted kidneys (Sadowski et al., 2005, Thoeny et al., 2006). All these explorations underscore the growing scope of T₂* sensitized renal MRI and its value for the noninvasive assessment of renal oxygenation and perfusion.

From qualitative to quantitative interpretation of renal BOLD-MRI

Notwithstanding its potential to qualitatively probe renal oxygenation, the validity of the argument about the T₂*/pO₂ relation and efficacy of BOLD-MRI for quantitative and spatiotemporal characterization of renal tissue perfusion and oxygenation under various functional conditions requires further research. While it is a widely accepted notion that renal BOLD-MRI is qualitatively related to tissue pO₂ the link between T₂* and renal tissue pO₂ is also recognized to be susceptible to the oxyHb dissociation curve, the haematocrit, and the

vascular volume fraction (Ogawa, 2012, Griffeth and Buxton, 2011, Evans et al., 2008b, Evans et al., 2007, Evans et al., 2008a). This added complexity creates a challenge for interpreting BOLD weighted MRI and parametric T_2^* mapping data (Michaely et al., 2012, Fine and Dharmakumar, 2012, Inoue et al., 2012, Evans et al., 2007).

With this in mind it is not as much of a surprise – as it might appear at first glance – that an unambiguous physiological interpretation of renal T_2^* requires a calibration with gold standard quantitative physiological measurements including renal tissue pO_2 . This has largely remained elusive due to constraints dictated by MR compatibility and MR safety requirements and by practical obstacles and technical challenges associated with probe implementation within an MR system. A very limited number of studies attempted to investigate the link between established invasive methods and T_2^* -weighted MRI (Juillard et al., 2004, dos Santos et al., 2007, Li et al., 2009). These studies primarily relied on a comparison of MRI with invasive physiological measurements using independent cohorts of animals (dos Santos et al., 2007, Li et al., 2009). Alternatively, T_2^* and tissue pO_2 were monitored sequentially in the same animal with the limitation that data acquisition was applied at different times (Warner et al., 2011). The literature shows a singular study which reports simultaneous monitoring of renal R_2^* and tissue pO_2 (Pedersen et al., 2005). For this purpose the fraction of inspired oxygen (FiO_2 range: 5-70%) was modulated in pigs. The authors reported R_2^* changes to be linearly related with tissue pO_2 changes. Arguably, this conclusion appears somewhat premature, since T_2^* was recorded in the contralateral kidney while the pO_2 probe was positioned in the ipsilateral kidney (Pedersen et al., 2005).

Realizing the challenges and opportunities of tracking invasive physiological parameters and MR parameters simultaneously for the same kidney, an integrated multi-modality approach designated as MR-PHYSIOL was recently employed (Pohlmann et al., 2013a, Pohlmann et al., 2014a). MR-PHYSIOL combines established invasive measurements including arterial pressure, total renal blood flow, local tissue perfusion and tissue pO_2 with

T_2^* mapping, T_2 mapping, and kidney size measurements deduced from anatomical or functional MR images (Pohlmann et al., 2013a, Pohlmann et al., 2014a). MR-PHYSIOL has been applied for detailing the relation between renal T_2^* and renal oxygenation by use of a series of reversible interventions including a hypoxia/recovery maneuver in rats (Pohlmann et al., 2014a). Setting FiO_2 to 8% induced arterial hypoxaemia. With arterial hypoxaemia tissue pO_2 declined gradually, most prominently in the medulla: within 7 minutes medullary tissue pO_2 had decreased by 96% and reached a steady state. T_2^* changes paralleled the changes in pO_2 , with T_2^* being reduced by 59% in the outer medulla and 37% in the inner medulla. Accordingly, hypoxia and recovery revealed a close medullary tissue pO_2/T_2^* correlation as illustrated in Figure 3. This finding indicates that relative changes in T_2^* qualitatively reflect changes in medullary tissue pO_2 induced by hypoxia which accords with the notion of the link between T_2^* , StO_2 , blood pO_2 , and tissue pO_2 .

Challenges with quantitative interpretation of renal BOLD-MRI

Notwithstanding the convincing results on the close medullary tissue pO_2/T_2^* correlation during the hypoxic challenge, the notion that tissue pO_2 and T_2^* are closely correlated *per se* for all renal layers and in various (patho)physiological scenarios might be premature. Haematocrit, oxyHb dissociation curve, and vascular volume fraction are well-known confounders of the T_2^* to tissue pO_2 relation and call for a careful scrutiny of this relation for all renal layers under various (patho)physiological scenarios and the necessity for calibration of T_2^* sensitized MRI for probing renal oxygenation and perfusion.

Absolute regional renal T_2^ versus tissue pO_2 levels under physiological conditions*

Perhaps stating the obvious, absolute renal T_2^* does not reflect tissue pO_2 . Absolute values of renal T_2^* in healthy rodents have been consistently found to be higher in the inner medulla versus the outer medulla and cortex as demonstrated in Figure 4b (Ries et al., 2003,

Rognant et al., 2011, dos Santos et al., 2007, Pohlmann et al., 2013b, Arakelyan et al., 2013, Pohlmann et al., 2014a). These findings do not match tissue pO_2 levels measured by invasive methods, which provided the lowest average pO_2 for the inner medulla (Lubbers and Baumgartl, 1997). One reason behind what seems to be a discrepancy at first glance is that T_2^* does not relate to the deoxyHb/oxyHb ratio, but to the absolute amount of deoxyHb per tissue volume. This observation indicates that T_2^* is sensitive to blood oxygenation but is also influenced by the blood vessel volume fraction and the local haematocrit. Vascular volume fraction and haematocrit are lowest in the inner medulla (Edwards et al., 2000). Also, water content in the inner medulla is higher than in the outer medulla and in the cortex (Hueper et al., 2013, Pohlmann et al., 2013b) as indicated by the high medullary signal in T_2 weighted images (Figure 4c) and by the higher apparent water diffusion coefficient (ADC) in the inner medulla versus outer medulla as shown in Figure 4d.

To generalize, the dependency of absolute renal T_2^* on the vascular volume fraction and haematocrit does not only preclude extrapolation of T_2^* obtained for one renal layer to another, but also from one species to another.

T_2^ and tissue pO_2 response to test interventions*

Utilising MR-PHYSIOL while exposing rats to brief interventions of hyperoxia/recovery, aortic occlusion/recovery and hypoxia/recovery revealed major differences in T_2^*/pO_2 correlations between the interventions (Pohlmann et al., 2014a).

Hyperoxia/recovery showed poor correlations for tissue pO_2 changes versus T_2^* changes. This finding is plausible since almost all of the available Hb in arterial blood is already O_2 saturated under normoxic conditions. Setting FiO_2 to 100% barely lifts StO_2 in arterial blood. However, this manoeuvre induces a substantial increase in pO_2 of arterial blood. This enhances the driving force for O_2 diffusion from vessels to tissue as well as from arteries to veins. As a consequence, the increase in renal tissue pO_2 is substantial while that of

T_2^* – attributable to increased venous StO_2 – is small.

For the aortic occlusion/recovery intervention a closer correlation between the relative changes of tissue pO_2 and T_2^* was reported as compared to hyperoxia/recovery (Pohlmann et al., 2014a). Still, aortic occlusion caused a rather modest decrease of 11% in cortical T_2^* while cortical tissue pO_2 revealed an 88% reduction as illustrated in Figure 5. In comparison, when using a spatially-resolved near-infrared spectroscopy (NIRS) setup (Grosenick et al., 2013) – which enables quantitative estimation of Hb concentration per tissue volume element and of StO_2 in the renal cortex – a decrease in StO_2 by approximately 40% was found (Figure 5) during aortic occlusion. Interestingly, NIRS detected a 30% decrease in the Hb concentration per cortical tissue volume within a few seconds after cessation of the arterial blood flow (Figure 5). MRI measurements revealed a 4% reduction in kidney size during aortic occlusion as shown in Figure 5.

These multi-modality data deduced from MR, from quantitative invasive measurements, and from NIRS facilitated an enhanced insight into the renal oxygenation and perfusion changes during aortic occlusion. Occlusion of the suprarenal aorta causes an abrupt interruption of blood flow into the kidney. At this early stage renal O_2 consumption remains unaltered though. This induces a rapid and massive reduction in renal tissue pO_2 , which lowers blood pO_2 and StO_2 in the intrarenal (micro-)vasculature due to consumption of O_2 in the face of ceased supply of O_2 . This deoxygenation of intrarenal Hb is made worse by a progressive rightward shift of the oxyHb dissociation curve during the occlusion due to intrarenal accumulation of CO_2 . With the onset of aortic occlusion, outflow of blood via the renal vein lowers the intrarenal blood volume. This is evident from the drop in the Hb per tissue volume recorded by NIRS (Grosenick et al., 2013) and manifests itself in the immediate decrease in kidney size detected with MRI (Pohlmann et al., 2014a). Assuming that the total volume of the tubular, interstitial, and cellular compartments does not change, the blood volume fraction becomes markedly reduced. Consequently, the reduction in blood volume

fraction compensates most of the T_2^* changes induced by increased deoxyHb blood concentration (Figure 5). Hence the decrease in T_2^* is much smaller than the actual change not only in tissue oxygenation but also in blood oxygenation.

Hypoxia/recovery yielded the strongest renal medullary tissue pO_2/T_2^* correlation (Figure 3). The correlation was even closer than that observed for aortic occlusion/recovery (Pohlmann et al., 2014a). The pO_2 decrease obtained during hypoxia (FiO_2 8%) was not as fast as during aortic occlusion. Also, cortical pO_2 decrease was less pronounced than the decline in pO_2 obtained for aortic occlusion. Contrary to the pO_2 response, the T_2^* decrease during hypoxia was much more pronounced than that during aortic occlusion. It stands to reason that aortic occlusion must reduce intrarenal blood oxygenation much more and more rapidly than hypoxia. Also, intrarenal pCO_2 increases during occlusion due to CO_2 accumulation, but decreases during hypoxia due to hyperventilation induced by systemic hypoxemia (Marshall and Metcalfe, 1989). Decreased pCO_2 shifts the oxyHb dissociation curve to the left so that at given pO_2 the StO_2 is increased. Opposite effects are induced by increased pCO_2 . Taking these considerations into account, the T_2^* decrease during aortic occlusion should be more pronounced compared with hypoxia. This expectation is not confirmed by the experimental findings. The response of T_2^* to hypoxia using a FiO_2 of 8% overestimates the actual degree of blood (and tissue) hypoxia. The observed decrease in renal conductance during hypoxia indicates that renal vasoconstriction results in a reduction in intrarenal blood volume (Pohlmann et al., 2014a). Yet the vasoconstriction-related reduction in renal blood volume during hypoxia is most likely smaller versus the outflow-induced reduction in renal blood volume during aortic occlusion. Intriguingly, experimental findings derived from MR-PHYSIOL showed that the kidney size decreased more during hypoxia than during occlusion (Pohlmann et al., 2014a). This observation highlights an additional volume loss of renal tissue compartments other than the blood volume fraction during hypoxia. Contrary to aortic occlusion – where glomerular filtration ceases and along with it the

pressure gradient that drives tubular fluid toward the renal pelvis – filtration and tubular fluid flow will decrease but not cease during hypoxia. The outflow of tubular fluid causes a reduction in the tubular volume. Moreover, reabsorbed fluid cannot be drained by peritubular capillaries during occlusion because of the arrested blood flow. Consequently, the sum of the tubular plus the interstitial volumes remains unchanged. The situation is different during hypoxia where peritubular capillary blood flow is not arrested. In this case, reabsorbed fluid continues to be drained from the interstitium. Since the decrease in tubular volume is not counterbalanced by an increase in the interstitial volume, the sum of both volumes decreases. This translates into a larger decrease in the blood volume fraction during occlusion versus hypoxia, which might explain the discrepancies in the T_2^* and pO_2 response to hypoxia and aortic occlusion.

To generalize, differences in the T_2^* and pO_2 responses to reversible maneuvers of hyperoxia, aortic occlusion and hypoxia lead to the conclusion that plain translation of quantitative results observed for one intervention of renal hemodynamics and oxygenation to another intervention is not appropriate. T_2^* may not accurately reflect blood oxygenation and may be confounded by vascular and tubular volume fraction under certain (patho)physiological conditions.

Inter-layer heterogeneity of T_2^/pO_2 relation*

Arguably, the notion that pO_2/T_2^* correlations obtained for specific renal regions can *per se* be extrapolated to other renal areas is somewhat premature (Pedersen et al., 2005). Major inter-layer differences in the T_2^*/pO_2 correlations together with large differences in the linear regressions of T_2^*/pO_2 in response to hyperoxia/recovery, occlusion/recovery, and hypoxia/recovery were reported from MR-PHYSIOL (Pohlmann et al., 2014a). For example, significant Spearman rank correlations between medullary T_2^* and tissue pO_2 were observed for hypoxia/recovery (Figure 3), but – unlike the medulla – the cortex revealed the weakest

T_2^*/pO_2 Spearman rank correlations and no significant linear correlation for the T_2^*/pO_2 response to hypoxia and recovery (Figure 6). To generalize, the stark inter-layer differences underline the need for due caution when extrapolating spatiotemporal T_2^*/pO_2 changes obtained for specific renal regions to other renal areas.

T_2^ response to iodixanol contrast medium*

Intra-renal hypoperfusion and hypoxia are key elements in the pathophysiology of x-ray contrast-induced AKI. This hypothesis is based upon a number of animal studies that used invasive techniques to assess renal perfusion and oxygenation (Liss et al., 2009, Liss et al., 1998, Seeliger et al., 2007, Heyman et al., 1991, Lancelot et al., 2002, Seeliger et al., 2014b, Seeliger et al., 2014a). Studies using BOLD-MRI confirmed that contrast medium (CM) administration affects renal oxygenation (Arakelyan et al., 2013, Li et al., 2014, Ji et al., 2010). Intra-arterial administration of the high viscous CM (iodixanol) resulted in a transient increase in cortical T_2^* of up to 20%. Twenty minutes after CM administration the initial change in T_2^* was followed by a sustained decrease of about 10% below the pre-CM level (Figure 7) (Arakelyan et al., 2013). This T_2^* behaviour revealed striking differences when compared with invasively measured cortical tissue pO_2 as illustrated in Figure 7. The initial overshoot in T_2^* observed for rats (Arakelyan et al., 2013) and pigs (Haneder et al., 2012) was not found for cortical tissue pO_2 (Seeliger et al., 2007, Seeliger et al., 2014a). Moreover, whereas cortical T_2^* dropped only slightly below baseline (10%) cortical pO_2 was found to be reduced by about 40% (Seeliger et al. 2014a). This mismatch between T_2^* and tissue pO_2 changes can be attributed, at least in part, to a decrease in the vascular volume fraction. Contrast medium-induced high tubular fluid viscosity results in an increase in the intra-tubular pressure (Ueda et al., 1993, Seeliger et al., 2010). This pressure distends the tubules, which compresses intrarenal vessels due to the rather rigid renal capsule. The marked swelling of the kidney upon CM administration (Figure 7) most likely reflects the distension

of tubules. Data on the amount of Hb per cortical tissue volume obtained by NIRS corroborate the decrease in the vascular volume fraction (Figure 7). Another mechanism which contributes to the decrease in the vascular fraction is vasoconstriction (Seeliger et al., 2007) as indicated by the reduction in cortical vascular conductance (Figure 7). An additional effect that has a share in the disparities between T_2^* and tissue pO_2 is the CM-induced leftward shift of the oxyHb dissociation curve (Kim et al., 1990). The impeded release of O_2 from Hb decreases tissue pO_2 but increases (venous) StO_2 , which induces an increase in T_2^* .

To generalize, these results indicate that T_2^* underestimates CM-induced intra-renal hypoxia, mainly because of the decrease in the vascular volume fraction induced by an increase in tubular volume fraction and by vasoconstriction.

*Chronic kidney disease and renal T_2^**

Renal tissue hypoperfusion and hypoxia are generally deemed an important mechanism in the progression from AKI to CKD. It may therefore appear surprising that a recent large scale patient study using T_2^* mapping at magnetic field strengths of 1.5 T and 3.0 T reported no correlation between estimated GFR and medullary and cortical T_2^* for chronic kidney diseases (Michaely et al., 2012). Furthermore, medullary and cortical T_2^* were not related to gender and age (range 21-92 years) (Michaely et al., 2012). The authors concluded, that T_2^* mapping of a non-specific patient population is not able to discriminate between patients with different stages of CKD of various origins (Michaely et al., 2012). Irrespective of the heterogeneity of the patient cohort, the discrepancy between estimated GFR and renal T_2^* does not argue against intra-renal tissue hypoxia as a culprit in the development of CKD. With reduced GFR tubular reabsorption and renal O_2 consumption also become reduced. Whether or not intra-renal oxygenation decreases depends primarily on the degree of reduction in renal perfusion and O_2 delivery as compared to changes in GFR and O_2 consumption (Blantz and Deng, 2007). Unfortunately, renal perfusion was not assessed in the

study on CKD patients (Michaely et al., 2012). Recent MR-PHYSIOL findings provided a valuable contribution to the ongoing debate on the relationship between T_2^* and total renal blood flow (Pohlmann et al., 2014a). For the T_2^* to RBF relation significant Spearman correlations were deduced in response to hyperoxia/recovery, hypoxia/recovery and aortic occlusion/recovery. T_2^*/RBF correlations were even superior to those between T_2^* and tissue pO_2 . Keeping in mind that T_2^* provides a surrogate for blood oxygenation rather than tissue pO_2 (Evans et al., 2007) there is a lucid explanation for this remarkable finding. Tissue pO_2 primarily reflects the balance between O_2 supply and O_2 demand. Because of O_2 shunt diffusion, blood pO_2 and StO_2 in larger arterial and venous vessels exceed those in the capillaries as well as tissue pO_2 . The amount of O_2 that is shunted depends not only on O_2 consumption but also on arterial O_2 content and RBF (Blantz and Deng, 2007, Evans et al., 2011a, Evans et al., 2013). To summarize, for a clinical assessment of renal oxygenation it is prudent to supplement BOLD MRI with MR based RBF measurements.

Factors confounding renal T_2^*

It is sensible to state that T_2^* is directly related to the amount of deoxyHb per tissue volume and hence correlated with tissue pO_2 via blood pO_2 and the oxyHb dissociation curve. The recent findings on the correlation between T_2^* and tissue pO_2 revealed discrepancies that point at factors other than the known shifts of the oxyHb dissociation curve and changes in haematocrit, which may also confound the renal $T_2^*/tissue\ pO_2$ relationship. The T_2^* to tissue pO_2 correlation differences between interventions of hyperoxia, hypoxia and aortic occlusion together with the renal vascular conductance and kidney size data obtained by MR-PHYSIOL indicate that changes in the blood volume fraction considerably influence renal T_2^* . Changes in renal vascular conductance point at changes in intrarenal blood volume. This occurs via passive circular distension of vessels following changes in the transmural pressure gradient, or by active vasomotion.

Alterations in kidney size may be induced by volume changes in any of the renal fluid compartments. Besides the vasculature, the interstitial and the tubular compartments could also experience rapid volume changes and could therefore modulate the blood volume fraction. The tubular volume fraction is a unique feature of the kidney; it is quite large and can rapidly change due to (i) changes in filtration, (ii) alterations in tubular outflow towards the pelvis, (iii) modulation of the transmural pressure gradient, and (iv) changes in resorption.

Detailing the impact of changes in renal hemodynamics, tissue oxygenation, vascular and tubular volume fractions on T_2^* under various (patho)physiological conditions certainly requires a more sophisticated approach including insights from modeling the T_2^* signal in voxels using multi-compartment models or Monte-Carlo simulations (Zhang et al., 2014). En route towards a comprehensive model Figure 8 provides a schematic survey on the potential contributions of several confounders to T_2^* . These include changes in (i) the tubular compartment, (ii) the intrarenal vascular compartment, and (iii) Hb concentration per blood volume (haematocrit). Aortic occlusion (or that of the renal artery) results only in moderate reduction of renal T_2^* as illustrated in the empirical model shown in Figure 8. Figure 8 also illustrates a massive T_2^* reduction following occlusion of the renal vein. Simultaneous occlusion of the renal vein and artery causes an intermediate T_2^* reduction as pointed out in Figure 8. In each of these three cases, tissue pO_2 , blood pO_2 , and StO_2 approach zero. Yet the vascular volume fraction is reduced in case of arterial occlusion, increased in case of venous occlusion, and unchanged in case of the common arterio-venous occlusion. As also illustrated in Figure 8, vasodilation causes a T_2^* decrease due to an increase in the vascular volume fraction, although renal tissue pO_2 , blood pO_2 , and StO_2 increase due to improved O_2 delivery. Vasoconstriction induces an increase in T_2^* despite reduced O_2 delivery due to reduction in vascular volume fraction. Distension of tubules (e.g. induced by x-ray contrast media) results in increase in T_2^* in the face of primarily unchanged StO_2 , blood and tissue pO_2 due to reduced vascular volume fraction (Figure 8). Anaemia or an increase in plasma skimming

evoke an increase in T_2^* despite the drop in O_2 delivery and tissue pO_2 (Figure 8). Finally, changes in the inspiratory O_2 fraction change renal T_2^* . Hypoxia decreases T_2^* in parallel with StO_2 , blood and tissue pO_2 . The effect of hyperoxia on T_2^* is small.

Future directions for pushing the limits of renal MRI

The recognition that renal T_2^* does not quantitatively mirror renal tissue oxygenation in several (patho)physiological conditions and that T_2^* may not reflect blood oxygenation quantitatively in some scenarios should induce due caution for quantitative interpretation of BOLD-MRI. This recognition must not discourage clinical and basic scientists to make good use of the capabilities of BOLD-MRI. On the contrary, it should attract talent and resources for refining and perfecting the potential of the next generation of renal MRI methodology with the goal to further quantitative interpretation of BOLD-MRI. Explorations into the renal response to a specific (patho)physiologic scenario or pharmacologic paradigm should include quantitative data on the $T_2^*/$ tissue pO_2 relation using experimental approaches similar to MR-PHYSIOL. The information deduced from such a multi-modality approach is instrumental if not essential to interpret changes in renal oxygenation and perfusion, based upon changes in T_2^* alongside changes in physiological parameters. Admittedly, this approach is only feasible in animal models. Notwithstanding this limitation, this review aims at encouraging pioneers and early adopters interested in pursuing renal BOLD MRI in clinical settings including patients with AKI or CKD. Yet, it sets a gentle reminder that it is prudent to supplement BOLD-MRI with MR-based assessment of renal perfusion.

Deciphering the relation between regional renal T_2^* and tissue pO_2 – including the role of the T_2^* confounders vascular volume fraction, tubular volume fraction and oxyHb dissociation curve – requires further research. To be rendered a quantitative physiological approach, BOLD-MRI needs to be calibrated with established quantitative physiological measurements (marked in light blue in Figure 9). With this in mind Figure 9 attempts to

provide a basic scheme of an integrative approach that makes good use of the capabilities of magnetic resonance, physiological measurements and near infrared spectroscopy. Productive engagement in this area carries on to drive further developments including validation and calibration of MR with the ultimate goal to provide quantitative means for interpretation of renal hemodynamics, renal oxygenation, renal blood volume fraction and tubular volume fraction related parametric MRI (Figure 9). This requires that renal blood oxygenation level associated T_2^* changes need to be differentiated from T_2^* changes induced by changes in the T_2^* confounders tubular and vasculature volume fraction (marked in red in Figure 9). To meet this goal the renal MRI portfolio needs to entail T_2^* mapping to probe for changes in blood oxygenation level but also T_2 mapping and proton density imaging to monitor net water changes and fluid shifts (marked in dark blue in Figure 9). T_2 mapping would also help to discriminate the susceptibility induced contributions (T_2') from the T_2 relaxation contributions to T_2^* . For this purpose it is also appealing to pursue quantitative susceptibility mapping (QSM). QSM provides a novel MR contrast mechanism to determine apparent magnetic susceptibility in tissue, which is useful for identification of BOLD contributions. Arguably, the potential of renal QSM is as yet untapped, with an early application being intriguing but limited to *ex vivo* investigations (Xie et al., 2014).

For a comprehensive characterization of renal oxygenation and perfusion it is prudent to include MR assessment of renal blood volume (RBV) using intravascular contrast agents such as ultrasmall superparamagnetic iron oxide (USPIO) based agents (Wang et al., 2013, Storey et al., 2011) to probe for vasodilation, vasoconstriction and other changes in the blood volume fraction as illustrated in Figure 9. For this purpose it is essential to first study the renal oxygenation and perfusion response to the intravascular administration of USPIOs using established physiological *in vivo* measurements in order to offset, for instance, concerns regarding USPIO application in patients with potentially compromised kidney function. Admittedly, the use of USPIOs for RBV assessment runs the caveat that the USPIO induced

T_2^* changes might interfere with T_2^* changes caused by the BOLD effect. For example, it is fair to assume that following administration of USPIO the balance of the two competing T_2^* effects during aortic occlusions (changes in deoxyHb vs. decrease in RBV) is shifted in favour of the sensitivity to RBV changes due to the strong T_2^* effect of iron oxides (Pohlmann et al., 2014b). The tubular volume fraction can be scrutinized with apparent water diffusion coefficient (ADC) determination or intra-voxel incoherent motion techniques (Hueper et al., 2013, Eckerbom et al., 2013, Zhang et al., 2012a, Ichikawa et al., 2013, Niendorf et al., 1996) (Figure 9). Arterial spin labeling MR techniques provide means for MR based assessment of renal perfusion (Wang et al., 2012, Zhang et al., 2012a) and can be used for examination of regional renal blood flow (Liu et al., 2012).

The need for solving the renal oxygenation and perfusion conundrum can be expected to continue to spur and drive technological MR developments. Fluorine MRI (^{19}F MR) is an innovative technology which provides an alternative for probing renal blood volume and for assessing renal tissue $p\text{O}_2$ or renal blood $p\text{O}_2$ (Figure 9) as demonstrated in recent feasibility studies (Liu et al., 2011, Hu et al., 2013). For this purpose ^{19}F perfluorocarbon nanoparticles can be measured directly *in vivo* in rather sparse concentrations (Hu et al., 2013). The specific advantages emerging from the use of ^{19}F MR are twofold: a virtual absence of ^{19}F in the body tissues yielding background free images with complete signal selectivity and a possibility to quantify the ^{19}F MR signal with spectroscopy. Arguably, it is too early to make ultimate statements since renal ^{19}F MR is still in its infancy and the potential of renal ^{19}F MR is as yet untapped. Yet recent preliminary reports on the capabilities of ^{19}F MR of the kidney and radiofrequency coil developments for ^{19}F MR are heartening (Waiczies et al., 2013, Pohlmann et al., 2014c). ^{23}Na MRI is another emerging heteronuclear MR tool to examine renal sodium content in small rodents and in humans (Haneder et al., 2014, Kalayciyan et al., 2013, Kopp et al., 2012).

The gain in intrinsic sensitivity and the linear relationship between magnetic field strength and microscopic susceptibility (Turner et al., 1993, van der Zwaag et al., 2009, Donahue et al., 2011, Meloni et al., 2013) renders it conceptually appealing to pursue renal MRI at ultrahigh magnetic field strengths (Niendorf et al., 2013, Niendorf et al., 2010). For all these reasons MR methodology established for human MRI needs to be carefully adapted to free breathing rodents and vice versa. These efforts should be designed to foster enhanced spatio-temporal resolution using state-of-the art parallel imaging (Niendorf and Sodickson, 2008, Niendorf and Sodickson, 2006b, Niendorf et al., 2005, Niendorf and Sodickson, 2006a), advanced MR pulse sequences (Klix et al., 2014), explorations into simultaneous T_2^*/T_2 sensitized MRI to reduce scan times (Fuchs et al., 2013), application of T_2^* mapping techniques free of image distortion (Niendorf, 1999, Heinrichs et al., 2009) and development of novel radiofrequency antennas to enhance the sensitivity of MR detectors (Dieringer et al., 2011, Thalhammer et al., 2012, Winter et al., 2012, Wagenhaus et al., 2012, Grassl et al., 2013, Graessl et al., 2014a, Graessl et al., 2014b).

On the invasive side, the probes incorporated in MR-PHYSIOL for total renal blood flow, local tissue perfusion and tissue pO_2 measurements could be complemented by intermittent blood samples to measure parameters such as haematocrit, pO_2 , Hb concentration, and StO_2 . This should shed further light into, e.g., the role of shifts in the oxyHb dissociation curve (Figure 9). A recent report also highlighted a novel approach that relies on implantation of fluorescence optodes in the femoral artery and renal vein to elucidate renal O_2 delivery and consumption (Abdelkader et al., 2014).

The development and application of multi-modality approaches continues to be in a state of creative flux. It is to be expected that future hybrid implementations may include optical imaging techniques such as NIRS. Notwithstanding its depth penetration constraints which at present limits its application to the renal cortex, NIRS has the potential to help characterize renal oxygenation. NIRS was applied to monitor changes of StO_2 and Hb

concentration per tissue volume in the kidney of rats after administration of contrast agents (Krause et al., 2002). With advanced NIRS approaches it is even possible to measure absolute values of Hb concentration and StO₂ which was demonstrated for the renal cortex of small animals (Grosenick et al., 2013). Other efforts push into the direction of characterizing renal perfusion by employing near infrared laser speckle imaging (Bezemer et al., 2010) or by detecting NADH autofluorescence (Raman et al., 2009).

To conclude, further explorations are essential before the quantitative capabilities of parametric MRI can be translated from experimental research to the clinic to improve our understanding of hemodynamics/oxygenation in kidney disorders. Moving T₂* sensitized MRI from the research area into the clinic remains challenging but has spurred the drive towards a comprehensive stand-alone MR protocol for assessment of renal haemodynamics and oxygenation. As parametric mapping of T₂* and other MR biomarkers become increasingly used in preclinical research and clinical science, they should help to further advance the potentials of MR for assessing kidney diseases.

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Conflict of interest

The authors have no conflict of interest to declare.

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Figure Captions

Figure 1:

Coronal views of rat kidneys: **a)** T_2^* sensitized MR image acquired *ex vivo* using an in-plane spatial resolution of $50\ \mu\text{m}$ (cortex COR; outer medulla OM; inner medulla IM), **b)** photograph of a freshly excised rat kidney, **c)** T_1 -weighted anatomical MR image acquired *ex vivo* using an in-plane spatial resolution of $50\ \mu\text{m}$, **d)** high spatial resolution x-ray image acquired *ex vivo*, **e+f)** modestly and heavily T_2^* weighted *in vivo* MR images acquired with an in-plane spatial resolution of $220\ \mu\text{m}$. The 1 cm scale bar illustrates the size of the rat kidney.

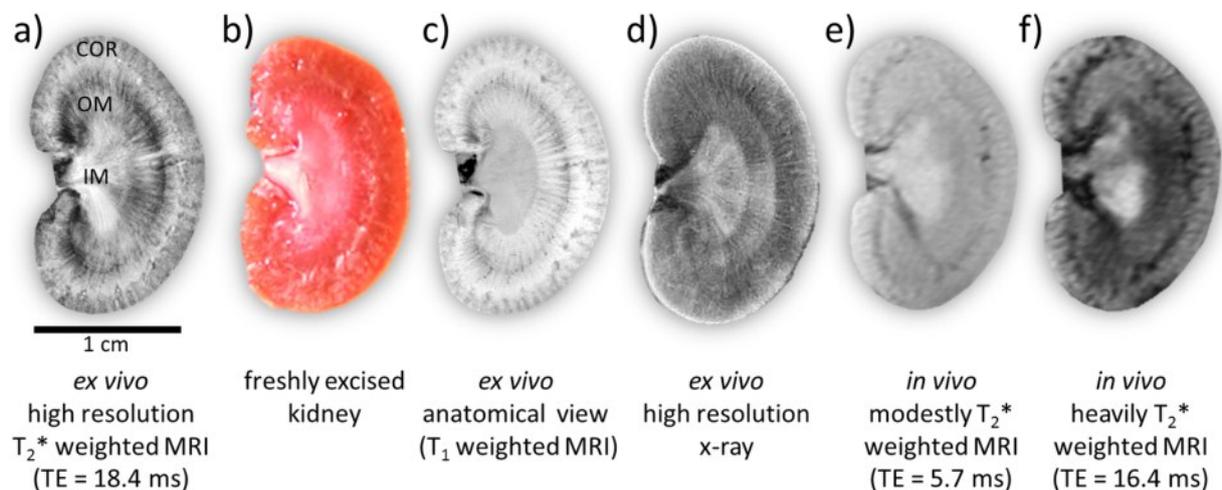


Figure 2:

Examples of T_2^* mapping based monitoring of **left**) ischemia and reperfusion, **center**) 3 min and 90 min after the injection of the contrast medium Iodixanol, and **right**) during brief periods of hypoxia and hyperoxia in rats. Shown are T_2^* difference maps of the kidney (colour-coded) between each intervention and the baseline image before the respective intervention.

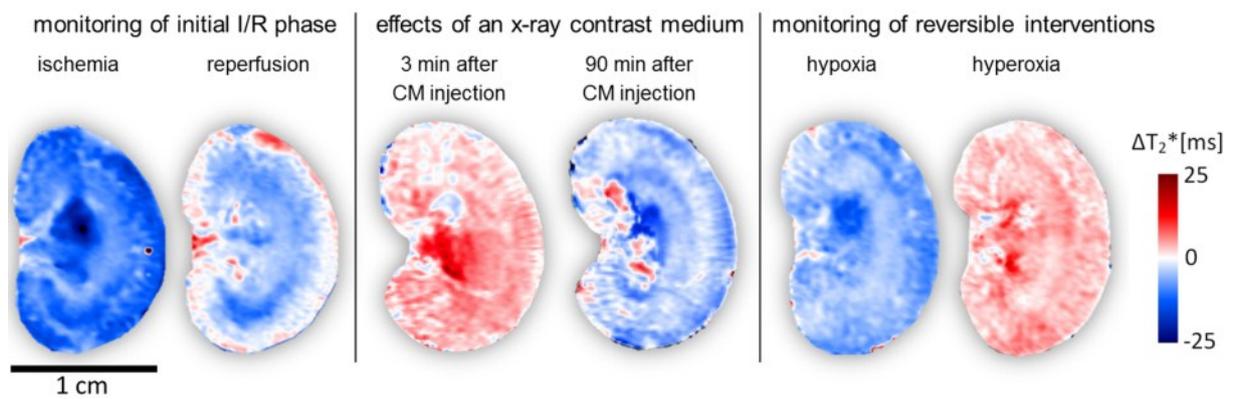


Figure 3:

Parametric correlation analysis (Pearson's analysis) and non-parametric correlation analysis (Spearman's analysis) between relative changes of outer medullary T_2^* and relative changes of medullary tissue pO_2 in response to a hypoxia & recovery maneuver. The coefficient of determination for Pearson (R_p^2) and the linear regression equation, and the Spearman coefficient (R_s^2) are given. Hypoxia & recovery revealed a strong medullary tissue pO_2/T_2^* correlation. These findings indicate that relative changes in T_2^* qualitatively reflect changes in medullary tissue pO_2 induced by hypoxia.

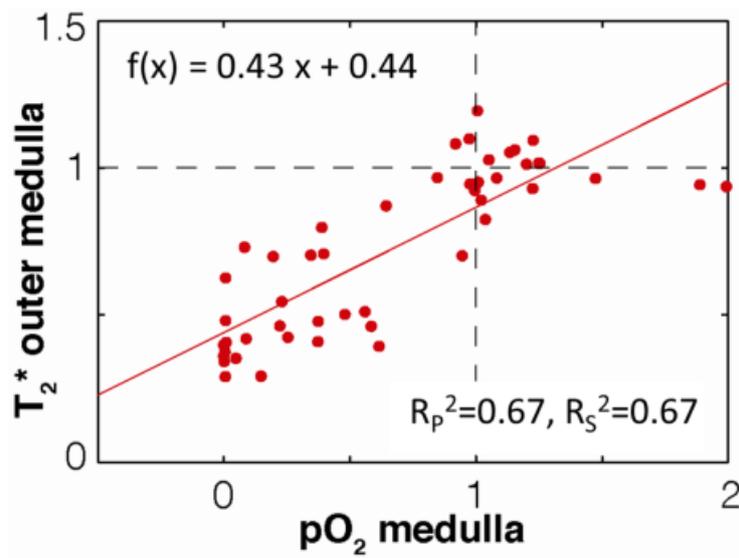


Figure 4:

Coronal views of a rat kidney acquired *in vivo* under physiological conditions baseline: **a)** T_2^* weighted MR image using an in-plane spatial resolution of $220\ \mu\text{m}$. The scale bar illustrates the size of the rat kidney. **b)** color coded renal T_2^* -map derived from a series of images acquired with different T_2^* weighting and an in-plane spatial resolution of $220\ \mu\text{m}$, **c)** T_2 weighted renal MR image (in-plane spatial resolution of $220\ \mu\text{m}$) and **d)** color coded map of the renal apparent diffusion coefficient (ADC) derived from a series of images acquired with different diffusion weighting and an in-plane spatial resolution of $220\ \mu\text{m}$. Absolute values of baseline renal T_2^* are higher in the inner medulla versus the outer medulla and cortex. T_2 in the inner medulla is higher than in the outer medulla and cortex, which indicates higher inner medullary water content, as confirmed by the higher ADC.

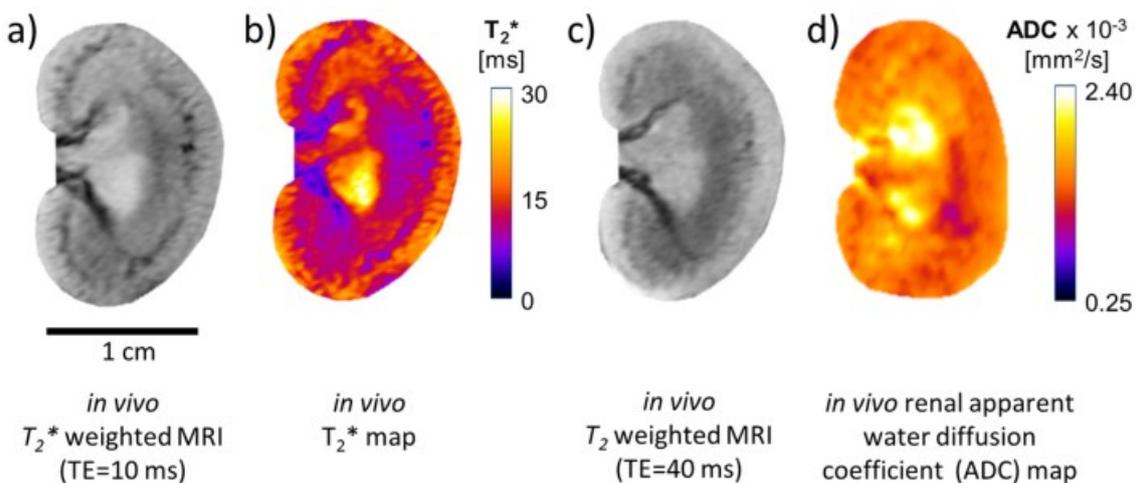


Figure 5:

Synopsis of changes in renal parameters which were observed in response to aortic occlusion. Changes in renal parameters were derived from MR-PHYSIOL including cortical T_2^* , kidney size, and cortical tissue pO_2 and from near infrared spectroscopy (NIRS) using time-domain NIRS setup equipped with three picosecond diode lasers (wavelength of 690 nm, 800 nm and 830 nm) and a multi-distance fiber probe which was positioned directly above the exposed rat kidney to determine cortical O_2 saturation of Hb and the cortical concentration of Hb per tissue volume. Aortic occlusion caused a rather modest cortical T_2^* decrease of 11%. MRI revealed a 4% reduction in kidney size during aortic occlusion. Cortical tissue pO_2 revealed an 88% reduction. Oxygen saturation of Hb derived from NIRS decreased by approximately 40%. Furthermore, NIRS detected a 30% decrease in the Hb concentration per cortical tissue volume upon aortic occlusion.

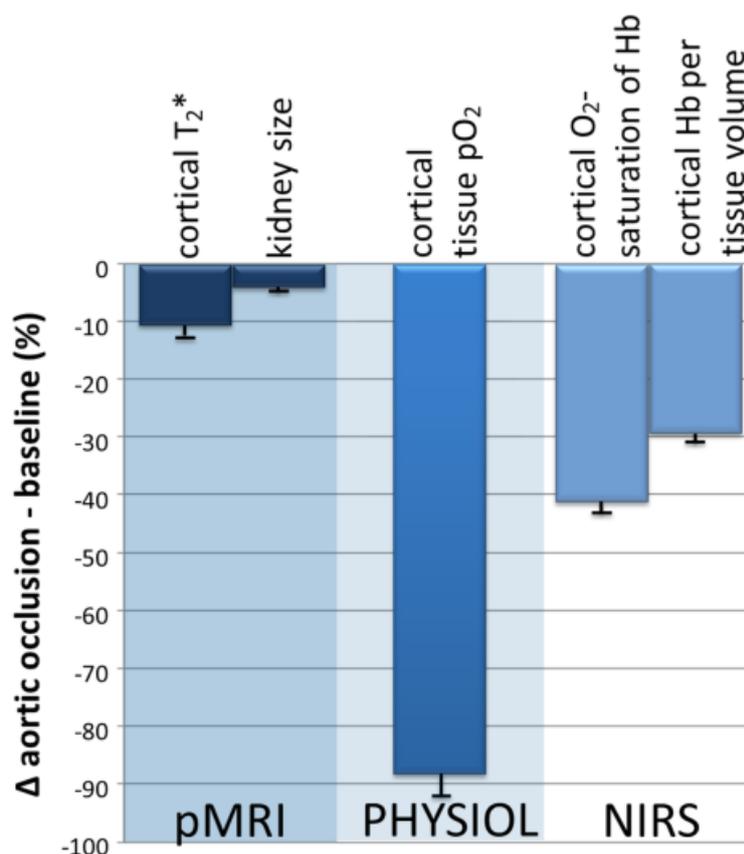


Figure 6:

Parametric correlation analysis (Pearson's analysis) and non-parametric correlation analysis (Spearman's analysis) between relative changes of cortical T_2^* and relative changes of cortical tissue pO_2 in response to a hypoxia & recovery maneuver. The coefficient of determination for Pearson (R_p^2) and for Spearman (R_s^2) is given. Unlike the medulla (see Figure 3) the cortex revealed very weak T_2^*/pO_2 Spearman rank correlations and no significant linear correlation for the T_2^*/pO_2 response to hypoxia & recovery.

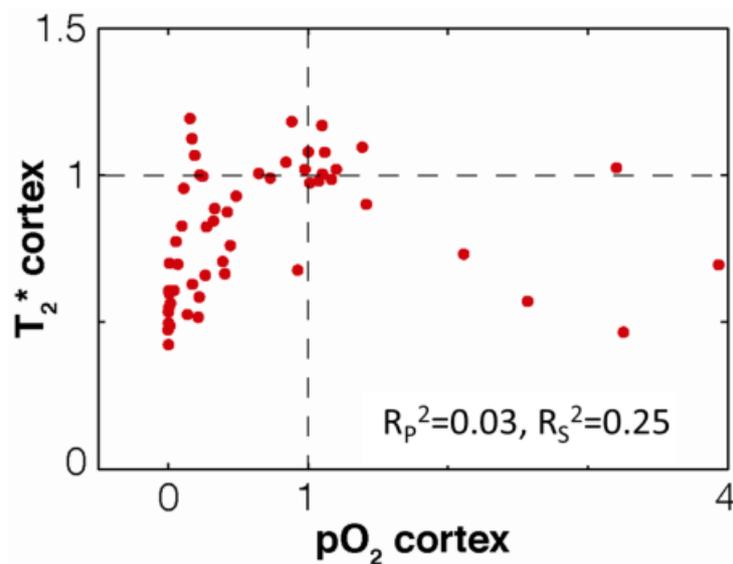


Figure 7:

Effects of administration of the x-ray contrast medium (CM), iodixanol 320 mg iodine/ml (1.5 ml bolus injection into the thoracic aorta) in rats. **Top:** T_2^* maps acquired before and 3, 10, 20, 30 and 50 min after CM administration. For comparison, a T_2^* map obtained during hypoxia (FiO_2 8%) is shown on the far right. **Bottom:** Time course of renal parameters (mean \pm SEM from cohorts of 10 to 13 animals) derived from parametric MRI (cortical T_2^* , kidney size), invasive physiological measurements (cortical tissue pO_2 , cortical vascular conductance) and from near-infrared spectroscopy (cortical Hb per tissue volume, cortical O_2 saturation of Hb). Within the first 10 min following CM administration a transient T_2^* increase of about 20% was observed in the cortex. During the same period CM resulted in marked swelling of the kidneys with a maximum increase of 7%. The transient increase in T_2^* was followed by a small decrease to about -10% of baseline. Cortical tissue pO_2 presented a decrease of about 40%. The amount of Hb per tissue decreased rapidly to about 75% of baseline within 60-90 s of CM administration, thereafter slowly regained baseline level. Cortical O_2 saturation of Hb showed a transient dip within the initial 90 s and started to slowly decrease after about 20 min.

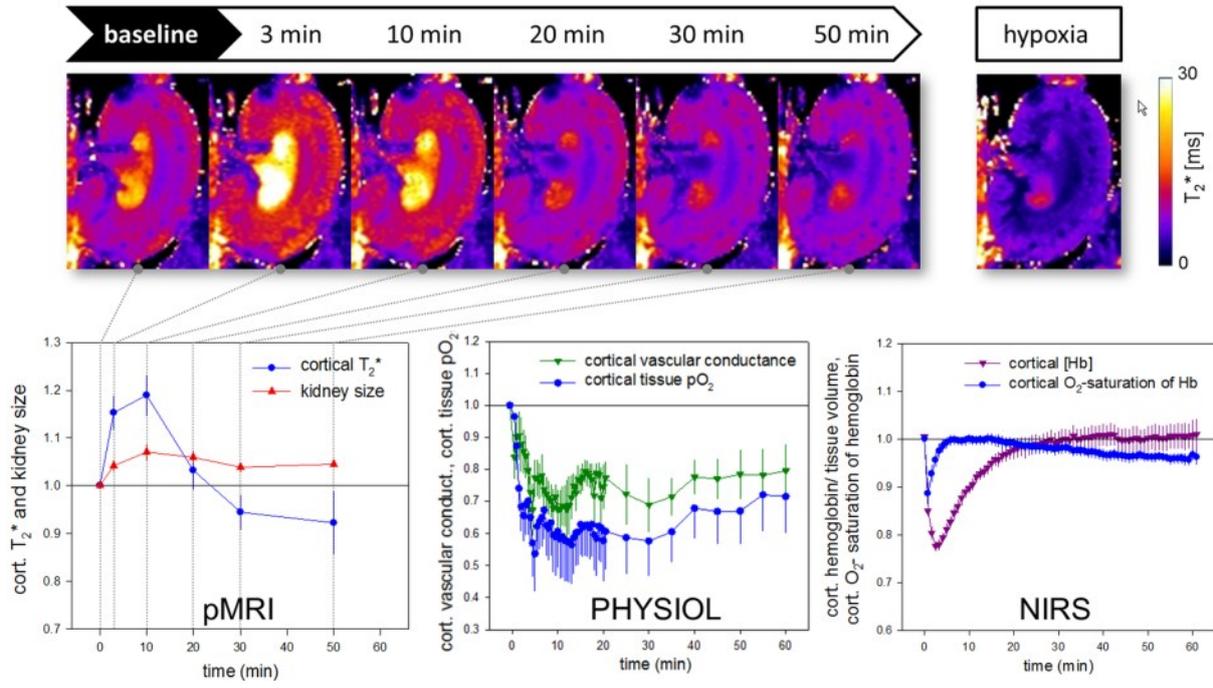


Figure 8:

Schematic overview of the key factors that govern renal T_2^* . This includes T_2^* alterations due to changes in the tubular compartment (represented by changes in their radius, r), the intrarenal vascular compartment (represented by changes in their radius, r), renal tissue pO_2 (tpO_2), blood pO_2 (bpO_2), haematocrit (Hct) and O_2 saturation of Hb (StO_2). The scheme depicts primary effects of the respective intervention/alteration only, not effects that represent the kidneys response to these changes. The amount of deoxygenated haemoglobin per tissue volume element (voxel) that is related to T_2^* is represented by the quantity of blue erythrocytes, the O_2 saturation of Hb is represented by the ratio of red-to-blue erythrocytes. Tissue pO_2 values are related to changes in O_2 delivery (due to changes in either haematocrit or StO_2) under the assumption that O_2 consumption is unchanged. Please note that the numbers given for T_2^* are not milliseconds but arbitrarily chosen numbers with baseline T_2^* set to 1.0.

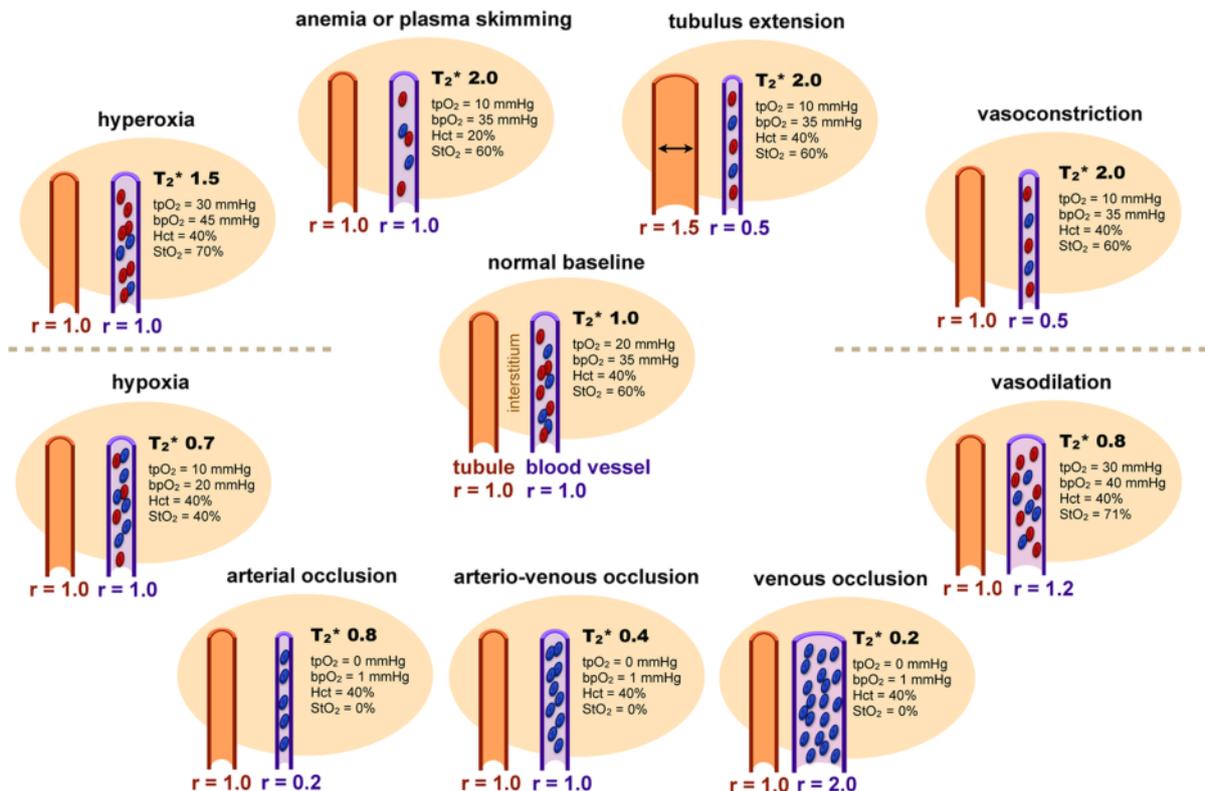


Figure 9:

Overview of an experimental concept customized to unravel the link between renal T_2^* and tissue pO_2 . This concept includes the role of the T_2^* confounding parameters vascular and tubular volume fraction, oxyHb dissociation curve and Hb concentration per blood volume (haematocrit), all marked in red. For a stand-alone MR protocol blood volume fraction, tubular volume fraction and oxyHb dissociation curve T_2^* contributions must be differentiated from renal BOLD T_2^* using standardized test procedures alongside with calibration with physiological measurements, all marked in light blue. These calibration efforts include a multi-modality approach that affords simultaneous acquisition of various MR parameters, invasively measured established physiological parameters, and parameters obtained by optical imaging techniques. To meet this goal an renal MR oximetry protocol is proposed which comprises blood oxygenation level dependent T_2^* and T_2 mapping, assessment of renal blood flow with arterial spin labeling MR, probing tubular water with diffusion weighted MRI, MR based kidney size measurements, detailing blood pO_2 with ^{19}F fluorine MRI and monitoring of renal blood volume with intravascular contrast agent enhanced MR. Renal oximetry needs to be calibrated by quantitative physiological measurements because of its qualitative nature. For detailed description and explanations see text.

