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Update on renal blood oxygenation level–dependent MRI to assess intrarenal oxygenation in chronic kidney disease

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Abstract

Identifying subjects with progressive chronic kidney disease will be important both in clinical practice and in conducting clinical trials. Pruijm *et al.* (in this issue) demonstrate for the first time that cortical oxygenation as evaluated by blood oxygenation level–dependent magnetic resonance imaging can predict future loss of renal function. These observations provide the necessary stimulus to continue the development of renal blood oxygenation level–dependent magnetic resonance imaging to further improve the sensitivity and specificity to renal oxygenation and hence the predictive power.

Chronic kidney disease (CKD) is considered to be an irreversible and usually progressive reduction in kidney function. However, only about one-half of individuals with CKD stage 3 will progress to end-stage kidney disease over 10 years.¹ The ability to identify subjects with progressive CKD is expected to have a major impact on clinical management and in enriching study populations for clinical trials. This has sparked interest in the discovery and development of novel biomarkers that may identify subjects with early CKD who are at risk of progression.

Although there are multiple causes for the development of CKD, the chronic hypoxia hypothesis was proposed as a common pathway for progressive CKD.² This hypothesis suggests that glomerular injury promotes microvascular obliteration with the loss of peritubular capillaries leading to hypoperfusion and reduced oxygen delivery. While the evidence of this hypothesis is strong in animal models, translation to humans has not been easy. A primary challenge has been the lack of a noninvasive method to monitor renal oxygenation in humans.

Blood oxygenation level–dependent magnetic resonance imaging (BOLD-MRI) is the only known *noninvasive* method to be sensitive to the oxygenation status of the kidneys that can be readily used in humans. It is based on the change in the magnetic property of hemoglobin based on its oxygenation status with deoxygenated hemoglobin being weakly paramagnetic. In the presence of deoxygenated hemoglobin, the random vascular distribution in tissue results in an effective magnetic field inhomogeneity leading to enhanced apparent T₂

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DISCLOSURE

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relaxation characterized by T_2^* . Earlier interest in the method was primarily directed at the renal medulla, which is known to naturally exist in a hypoxic milieu and BOLD-MRI is inherently more sensitive to hypoxic tissue.³ Renal BOLD-MRI signals are also influenced by hydration status, sodium avidity, vascular volume, vascular geometry, hematocrit, and factors affecting the oxygen-hemoglobin disassociation curve such as temperature and pH. These may be controlled or accounted for in acute experiments in which the effects of physiological and pharmacologic maneuvers are being studied. Many of the earlier studies were geared toward such acute experiments, and several of them were compared with invasive microprobe measurements of pO_2 in animal models.

The application of BOLD-MRI to patients with CKD has resulted in apparent inconsistent findings. Inoue *et al.*⁴ showed cortical T_2^* measures were correlated with the estimated glomerular filtration rate (eGFR), at least in nondiabetic subjects. Yin *et al.*⁵ showed a negative correlation in the cortex and a positive correlation in the medulla in terms of R_2^* ($= 1/T_2^*$) versus eGFR in patients with diabetic nephropathy. However, a study with a large number of subjects ($N= 280$) showed that BOLD-MRI was not correlated with eGFR.⁶ It should be noted that this study was not designed as a study of CKD. BOLD-MRI data were acquired for subjects already undergoing an abdominal MRI scan, for example, for staging of cancer in abdominal organs or MR angiography of renal or mesenteric arteries. The BOLD-MRI data were then correlated with a recent (within 14 days of the MRI scan) eGFR measurement obtained from the medical records. Clinical CKD classification is based on a persistent reduction in eGFR. A single eGFR estimate may not necessarily indicate CKD. There was no subject preparation or control for concomitant medications; also no control group was included.

The group of Pruijm *et al.* conducted an initial BOLD-MRI study with a standardized protocol for food and water intake in a sufficiently large number of subjects ($N= 95$) and still found no significant difference compared with controls. However, when the data were analyzed again with a more objective and semiautomated method, the renal cortex was found to be less well oxygenated in CKD compared with controls. The analysis also afforded a depth profile in the form of an R_2^* slope, which is a surrogate for the corticomedullary difference in oxygenation. While providing preliminary evidence of reduced oxygenation status in CKD, it is important to note that these observations did not fully validate the chronic hypoxia hypothesis. First, there is no way to appreciate whether tissue is actually “hypoxic” based on the current implementation of BOLD-MRI. Second, the theory actually suggested that the increased hypoxia was associated with *progressive* CKD.

As an extension of their previous studies, the new report by Pruijm *et al.*⁷ provides the first indication that the BOLD-MRI measurements may be predictive of *progressive* CKD. A longitudinal study was performed over 3 years. The baseline BOLD-MRI measures (cortical R_2^* and corticomedullary difference in R_2^*) were found to be significantly correlated with changes in eGFR over the next 3 years. High R_2^* values (>90th percentile) showed the highest eGFR slopes and were associated with 3 times greater adverse outcomes. Receiver operating characteristic curve analysis of adverse outcomes showed an area under the curve of 0.71 for cortical R_2^* and 0.80 for R_2^* slope. At the same time, proteinuria was found to be more strongly correlated with a change in eGFR and had an area under the curve

of 0.83. So the BOLD-MRI findings have to be put in perspective. While promising, these data should be only considered as a starting point that stimulates further studies to improve the sensitivity of BOLD-MRI measurements. Further, it is possible that BOLD-MRI measurements can be combined with other imaging (e.g., the presence of fibrosis by diffusion MRI) and conventional measures to improve the predictive power.

Despite its merits, the study by Pruijm *et al.*⁷ did have limitations. The observed changes in R_2^* were small. Whether this is due to confounding effects of lower blood volume and hematocrit deserves further investigation. Recent data with arterial spin labeling perfusion MRI show large reductions in perfusion, even in moderate CKD.⁸ This could indicate a reduced blood volume (or vascular density). Anemia is also common in CKD, specifically in CKD stages 3b through 5. Although the 12-layer concentric objects analysis method is highly objective, it does compromise the ability to study the medulla. Because the changes in the cortex and medulla in advanced stages of CKD can be different,⁵ the net effect of averaging over both of these regions can reduce the sensitivity of the method in the inner layers. Last, even though the etiology of CKD seemed to show differences in the rate of change in eGFR, the BOLD-MRI measurements did not show differences to the same extent. This may again point to the limited sensitivity of the technique as currently implemented.

The limitations of renal BOLD-MRI have been discussed in the literature. BOLD-MRI as currently implemented does not directly measure po_2 and so cannot characterize tissue as being hypoxic. The multiparametric dependence of the BOLD-MRI signal leads to confounding effects, especially when comparing cohorts such as CKD versus healthy controls. Furthermore, BOLD-MRI inherently assumes a fast equilibrium between blood and tissue compartments, which may not hold in disease. Despite these known limitations, a role for BOLD-MRI still exists given the fact that there is no other *noninvasive* method to evaluate renal oxygenation *in vivo*.

In light of the above, a reasonable question to ask is “Where do we go from here?” To start, we may need to determine whether cortical or medullary changes are more important in predicting the progression of CKD. There is limited evidence, at least in diabetic nephropathy, that the functional dependence is opposite in the 2 regions,⁵ that is, cortex may be less oxygenated while the medulla may be better oxygenated in advanced stages of CKD. Also, it is important to determine whether the sensitivity of BOLD-MRI can be improved by accounting for confounding effects. Given the efficacy of BOLD-MRI to assess acute changes, other “stress” tests similar to the response to furosemide should be considered. Water loading has been considered, but not extensively studied. Multiparametric approaches such as BOLD-MRI combined with perfusion and fibrosis imaging could provide additional predictive power.

A few years ago, there was a commentary and letters to the editor following the report by Michaely *et al.*⁶ with one asking “Is there no future for renal BOLD-MRI?” While the studies by Pruijm *et al.*⁷ did address many of the technical limitations of the previous study,⁶ there remains a need to address the fundamental issue of concomitant effects when applying renal BOLD-MRI to compare cohorts. Changes in renal oxygenation may be associated

with concomitant changes in vascular density and hematocrit whose contributions to the BOLD-MRI signal may not be additive, but actually competing (as depicted in Figure 1).

This potentially could explain the limited sensitivity of renal BOLD-MRI observed to date. A new model has been proposed that allows one to map R_2^* measurements to blood and tissue pO_2 with the knowledge of regional vascular density and hematocrit.⁹ Incorporating independent measures of vascular density may therefore allow for a more accurate evaluation of renal oxygenation. So, yes there is still a crucial role for renal BOLD-MRI to play in the evaluation of intrarenal oxygenation in CKD.

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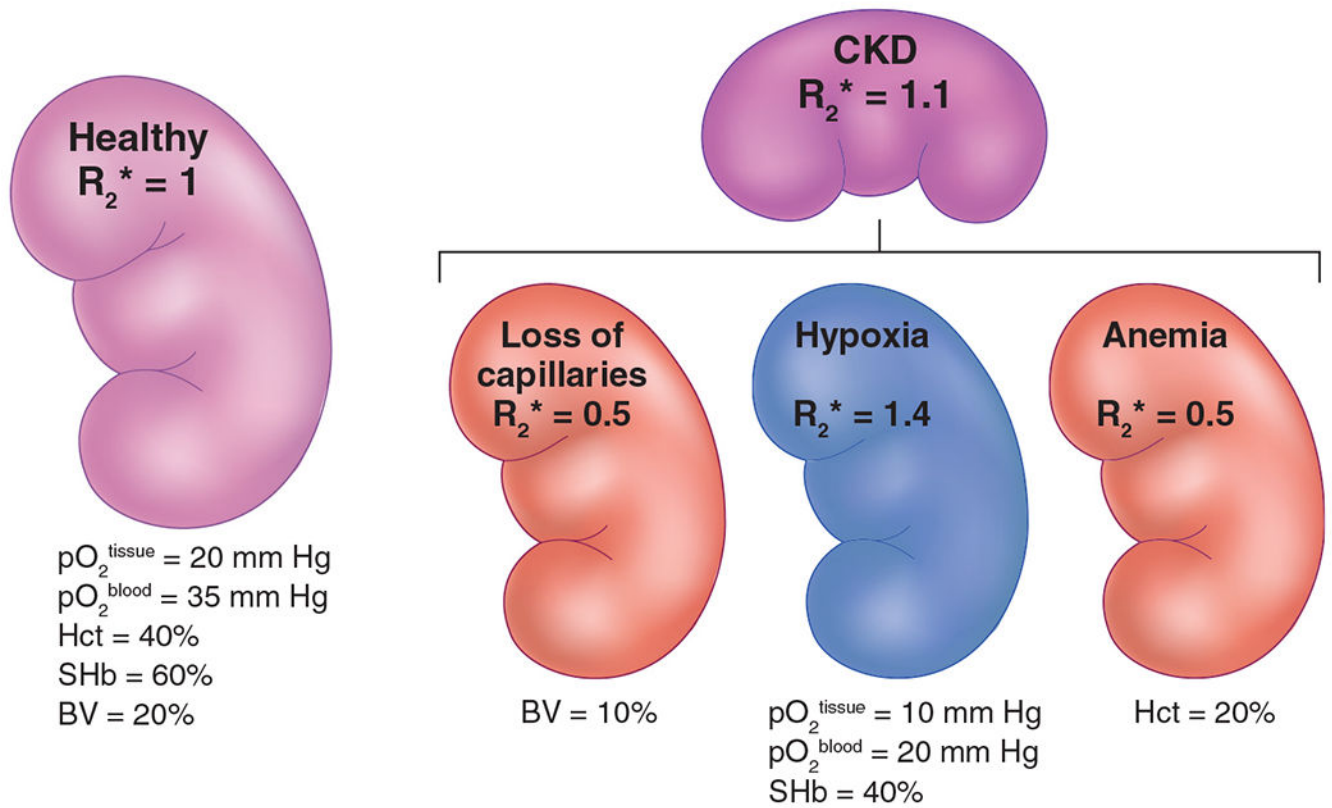


Figure 1 |. Schematic overview of the key factors that govern renal R_2^* .

This includes changes in renal blood pO_2 , hematocrit (Hct), O_2 saturation of Hb (SHb), and fractional blood volume (BV). Please note that all values given here are only for illustrative purposes. R_2^* values were also chosen for illustrative purposes, with healthy renal R_2^* set at 1.0. In chronic kidney disease (CKD), along with reduced tissue and blood oxygenation, there is loss of microvasculature and anemia. The net contribution makes the R_2^* in CKD only slightly higher compared with healthy controls.