Blood Oxygen Level Dependent Magnetic Resonance Imaging (BOLD MRI) analysis in Atherosclerotic Renal Artery Stenosis

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Abstract

Purpose of review—Blood Oxygen Level Dependent Magnetic Resonance Imaging (BOLD MRI) is a noninvasive tehnique evaluating kidney tissue oxygenation that requires no contrast exposure with the potential to allow functional assessment for patients with Atherosclerotic Renal Artery Stenosis (ARAS). Normal cortical-to-medulla oxygenation gradients are preserved in many patients treated for several years with medical antihypertensive therapy without restoring renal blood flow. The current review is of particular interest as new methods were applied to the analyses of BOLD MRI opening perspective of its wider utilization in the clinical practice.

Recent findings—Recent findings show that more severe vascular compromise ultimately overwhelms these adaptive changes, leading to overt cortical hypoxia and expansion of medullary hypoxic zones. "Fractional kidney hypoxia" method of analysis, developed as an alternative method of BOLD MRI analysis, avoids the assumption of discrete cortical and medullary values and decreases the bias related to operator selection of ROIs.

Summary—We believe that thoughtful application and analysis of BOLD MRI can provide critical insights into changes in renal function prior to the onset of irreversible renal injury and may identify patients most likely to gain from measures to reverse or repair disorders of tissue oxygenation.

Introduction

Atherosclerotic renal artery stenosis (ARAS) is a common finding in older patients and remains one of the most common causes of secondary hypertension and reduced kidney function. Severe occlusive ARAS activates pressor systems, and ultimately can lead to renal

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atrophy (1). The complexity of the renal circulation poses a particular challenge when defining the relationships between arterial blood flow and renal tissue oxygenation (2).

Remarkably, a decrease in renal blood flow (RBF) does not invariably lead to renal hypoxia, likely due to both a surplus of oxygenated blood and a parallel decrease in glomerular filtration rate (GFR) and oxygen consuming tubular reabsorption of sodium. Studies of intra-renal blood flow distribution emphasize that cortex and medulla can be regulated independently under some conditions (3). At some point, renal artery stenosis threatens the viability of the kidney and irreversible kidney injury can occur leading to loss of kidney function (4), tissue fibrosis and end stage kidney disease designated as "ischemic nephropathy"(5). Determining precisely the "no-return" point of occlusive vascular lesion remains an elusive goal.

Direct measurement of renal tissue oxygen tension (pO2) has been achieved experimentally using invasive microelectrodes, but is not readily applicable for human studies.

Blood Oxygen Level-Dependent Magnetic Resonance Imaging (BOLD MRI) is a noninvasive imaging method applied in recent years to examine regional tissue oxygenation within the kidney. While interpretation and application of this technology remains controversial, renal artery stenosis is intuitively an ideal indication for BOLD MRI investigation.

This review summarizes our current understanding of the use of BOLD MRI in renovascular disease.

BOLD MRI principle and validation

BOLD MRI is based on paramagnetic properties of deoxyhemoglobin, whereas oxyhemoglobin is diamagnetic. The presence of deoxyhemoglobin affects the T_2^* relaxation time of neighboring water molecules and in turn influences the MRI signal of T_2^*-weighted (gradient echo) images. The rate of spin dephasing R_2^* (= $1/T_2^*$) thereby is closely related to the tissue content of deoxyhemoglobin. Since the capillary blood oxygen tension (pO$_2$) is normally in equilibrium with the surrounding tissue, changes in R_2^* levels represent changes in tissue pO$_2$.

Parametric maps of R2* illustrate the R2* translation of renal structures and has been applied to focus selection of local ROIs and exclude artifacts induced by adjacent tissue outside the kidneys. **[FIGURE 1]** Typically, cortex can be identified by lower R2* values, while a gradient of higher R2* levels develops in the medullary sections (6-9) (**TABLE 1**).

Experimental swine data using oxygen sensing electrodes within renal cortical and medullary locations demonstrate tissue oxygen levels consistent with deoxyhemoglobin levels identified using BOLD MRI (10). Average levels of tissue oxygen tension in the animal models ranged from 50 – 55 mmHg in cortex to as low as 15 to 20 mmHg in the deep sections of the medulla with 45% to 50% fall in oxygen level moving from cortex to deep medullary regions.

Factors influencing tissue oxygenation signal intensity in BOLD MRI studies

Deoxyhemoglobin level and tissue oxygenation can be modified by renal blood flow changes, but also by tubular solute transport, hydration state, arteriovenous shunts, antihypertensive drugs, temperature, blood pH and hematocrit. Recently, it has been shown that the contribution of a water load to R2* can be important, especially in the renal cortex (11).

Tubular sodium transport and medications

Experimental studies using either microelectrodes or BOLD MRI, establish that furosemide acutely lowers medullary R2* (therefore lowering deoxyhemoglobin) as a function of inhibiting solute transport in the ascending limb of Henle's loop. Acetazolamide, a diuretic acting on the proximal tubule, induces little change in the medullary oxygenation (6, 10).

Renal Blood Flow

Renal blood flow (RBF) is higher than any other organ with respect to organ weight, consistent with its primary function for blood filtration. The kidney has minimal overall oxygen consumption reflected in the smallest net arteriovenous difference in oxygen tension (12). The largest portion of RBF is directed towards the cortical glomeruli. The anatomical structure of medulla with its functional requirement of large amount of oxygen generates a progressively hypoxic milieu. Nearly constant oxygen depletion in this region makes it particularly susceptible to ischemic injury. Cortical tissue oxygenation can be maintained relatively constant when RBF is decreasing and is independent of the changes in the renal oxygen consumption (13).

In ARAS, when a "critical" 70% to 80% degree of stenosis is attained, renal hypoperfusion leads to a cascade of events from activation of the renin-angiotensin system to the rarefaction of small renal vessels, kidney fibrosis, loss of function, and atrophy (1). Studies of oxygen delivery and consumption in animal model indicate that tissue oxygen levels are stable even if cortical blood flow is reduced by up to 40%, thanks to reduced filtration and oxygen consumption (14). Medullary oxygenation may be compromised during moderate to severe acute cortical ischemia even when medullary blood flow is maintained (15). Low medullary pO_2 reflects combined effects of reduced blood flow and increased oxygen consumption, as demonstrated using furosemide administration (10, 11). Local gradients of cortical and medullary oxygenation are closely regulated, but sometimes independently from each other. Numerous vasoactive systems intervene to compensate renal blood flow changes. In a rat model, for example, angiotensin II infusion produces a 40% decrease of cortical perfusion, but medullary perfusion can remain unchanged, apparently protected by prostaglandin E2 synthesis (16). Modification of arteriovenous shunting in response to changes in renal blood flow appear to maintain the oxygen tension and adjust local areas to blood supply, but also may render some focal regions more susceptible to hypoxia (14).

Comparison of 1.5 and 3T BOLD MRI to study kidney oxygenation

Studies comparing 1.5 and 3.0 Tesla magnetic fields indicate that BOLD MRI measurements at high field strength amplify differences between cortical and inner medullary regions of the kidney. The stronger magnetic field increases the sensitivity to deoxyhemoglobin acting as a natural contrast agent (2, 21).

Maneuvers that reduce oxygen consumption related to tubular solute transport (e.g. furosemide administration or water load) allow functional evaluation of transport-related activity as a determinant of tissue oxygenation (6, 11) .

Methods for analyzing BOLD MRI

Interpretation of BOLD MRI data related to renovascular disease processes has been challenging and we believe that failure to define meaningful interpretation has limited its application. Few studies describe precisely the BOLD MRI acquisition protocol, tissue volumes definition and quantification of the oxygenation level. Most often, images are sampled within a 5-8 mm thick axial, sagittal or coronal slice. Volume and slice orientation definition is important as what is represented as a bi-dimensional image corresponds in reality to tridimensional slice of renal parenchyma.

ROI selection

By convention, individual T2*-weighted images are selected to define regions of interest (ROIs) within the cortex and medulla. Most commonly, a single average R2* value for each region is determined, either from a single slice, or as the average of several samples and/or slices (8, 10, 17).

The ROIs can be limited to small regions (cortical or medullary) (6, 8, 10) or can encircle the entire kidney (17). Selection of local ROI's in diseased kidneys is subject to wide variation and sensitive to operator bias. Most analytical methods assign a single "best" or "mean" value for R2* associated with either cortex or medulla. In reality, levels of R2* vary gradually from the cortex to the medulla, reaching a "most hypoxic" zone in the deepest sections of medullary pyramids. Hence, the precision, and reproducibility of R2* values are affected by the size and location of ROI. Larger ROIs that include the entire medullary compartments may provide more representative and less variable mean values, but often include multiple medullary and cortico-medullary overlap zones with different hemodynamics. Small, selective ROIs are less vulnerable to volume averaging, but may be skewed by fluctuations caused by spatial and temporal heterogeneity in oxygen distribution within the kidney, particularly in the medulla.

Compartments model

To partially overcome these limitations, Ebrahimi et al.(18) developed a model assuming the R2* populations in cortex and medulla could be defined by two distinct mathematical distributions. Using this assumption, the R2* values were separated into two renal compartments by fitting the histogram of the R2* data acquired from a large ROI encompassing both cortex and medulla to the corresponding distribution functions. A single

numerical R2* value was assigned for cortex and another for medulla. The limitations of this method are related to medullary heterogeneity and to the reliability of the histogram curve depending on the amount of data available, which compromises the precision or accuracy when these are limited. When relatively highly oxygenated medullary regions do not differ from cortex, or when kidneys are severely diseased, these boundaries may be blurred.

"Fractional kidney hypoxia" method

Saad et al. (19) recently developed an alternative method of BOLD MRI analysis with the aim of avoiding the assumption of discrete cortical and medullary values and decreasing the bias related to operator selection of ROIs. The renal tissue oxygenation was evaluated in both essential hypertensive and ARAS patients using a method to depict "fractional kidney hypoxia" determined by measuring the percentage of voxels from the whole kidney ROI with R2* values above 30 $\sec^{-1}$ taking the average of all available slices. Levels of cortical oxygenation were similar to those from methods with small ROIs. Estimates of medullary deoxygenation using fractional kidney hypoxia were substantially higher in in post-stenotic kidneys and were demonstrably related to hemodynamic severity of vascular lesions. The response to furosemide in the stenotic kidney was markedly blunted as compared with the contralateral kidney, essential hypertension kidneys and previous studies. The variability of "fractional hypoxia" in 2-4 axial slices was substantial at baseline and after furosemide administration, while cortical R2* values were quite reproducible. We believe that this variability reflects true biological differences between functional zones with different deep medullary representation, particularly in diseased kidneys.

Application of Renal BOLD MRI

Human studies suggest that BOLD MRI could identify kidney alterations in different conditions: after administration of nephrotoxic contrast, allograft injury, water loading (11), and occlusive renal arterial disease (8). Some authors had postulated that local hypoxia is a "final common pathway" related to kidney injury. Surprisingly, normal or low deoxyhemoglobin in both cortical and medullary regions can be observed in conditions that severely limit tubular metabolic activity, such as acute interstitial inflammation associated with transplant rejection, acute tubular necrosis, or even renal atrophy beyond an occluded vessel (8, 20). BOLD MRI has been recently used to show that Angiotensin II receptor blocker could partially ameliorate intrarenal hypoxia in chronic kidney disease patients (21), whereas, blockade of renin-angiotensin system in patients with type 2 diabetes does not seem to increase renal tissue oxygenation (22).

Studies in hypertensive African Americans demonstrate higher R2* levels associated with increased medullary volume and sodium reabsorption as compared with Caucasian patients. These data support a role increased oxidative stress in African Americans that may accelerate hypertension and target organ injury (34).

BOLD MRI found a particular application in renal artery stenosis (RAS) having a direct consequences for intrarenal oxygenation. Warner et al. showed that graded reduction in blood flow acutely decrease tissue oxygenation measured by oxygen electrodes that also appear as changes in R2* signal, more pronounced in the medulla (23).

In our previous study, we found that in ARAS patients' compared with age-matched group of essential hypertensive patients, the cortical and medullary oxygenation was preserved despite significant reductions in blood flow in the stenotic kidneys sufficient to elevate plasma renin activity (7).

Another BOLD MRI study included three groups of patients: essential hypertension, "moderate" ARAS, and "severe" ARAS with Doppler velocities >384 cm/s and loss of functional renal tissue (8). Cortical R2* levels were significantly higher in severe ARAS group, showing the limits of kidney adaptation. BOLD analysis utilizing the "fractional hypoxia" method (19) confirmed that severe renovascular occlusion does indeed produce cortical hypoxia (FIGURE 1).

A separate publication from the United Kingdom in patients with ARAS used an analysis attributing a single average R2* value over entire coronal slice and showed that a higher level of R2* with preserved kidney volumes was associated with favorable response to renal revascularization (17).

Future Directions and Limitations

Despite its simplicity and appeal, clinical application of BOLD MRI is not yet standardized or routine. Some authors suggest that intrinsic limitations related to spatial distribution of blood and/or magnetic field non-homogeneities may limit the utility of BOLD MRI (24). In a recent publication Michaely et al. (25) failed to identify a correlation between R2* values and estimated GFR in patients with different stages of CKD in a large cohort with a variety of kidney diseases. However, these BOLD MRI studies were undertaken without standardized conditions such as control of sodium intake and defined medications (especially ACEI/ARBs or diuretics). Also, renal tissue oxygenation likely depends not only on the severity of CKD but also on the etiology of the underlying kidney disease (26).

Further studies of renal oxygenation over time and changes observed with medical therapy or revascularization in ARAS will be essential to define more precisely how variation in tissue oxygenation is related to tissue injury in this disorder. More precise definition of the level of oxygenation associated with renovascular occlusive disease may identify those patients most likely to benefit from renal revascularization, thereby clarifying results from negative treatment trials such as the ASTRAL and STAR trials (4, 27, 28).

Conclusion

We believe that BOLD MRI could be a valuable tool to evaluate changes in intra-renal oxygenation and potentially to identify kidneys at risk from vascular injury that may benefit from renal revascularization and/or adjunctive measures to repair the kidney before irreversible parenchymal damage.

Acknowledgments

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Key Points

- Blood Oxygen Level Dependent Magnetic Resonance Imaging (BOLD MRI) is the only noninvasive technique evaluating kidney tissue oxygenation.

- In Atherosclerotic Renal Artery Stenosis (ARAS) initial human studies showed a preserved cortical-to-medulla oxygenation gradients in many patients treated with medical antihypertensive therapy without restoring renal blood flow.

- More severe vascular compromise ultimately overwhelms kidney adaptive potential in some individuals, leading to overt cortical hypoxia and expansion of medullary hypoxic zones.

- New methods of BOLD MRI analysis will improve this evaluation sensitivity to detect changes in renal function prior to the onset of irreversible renal injury.
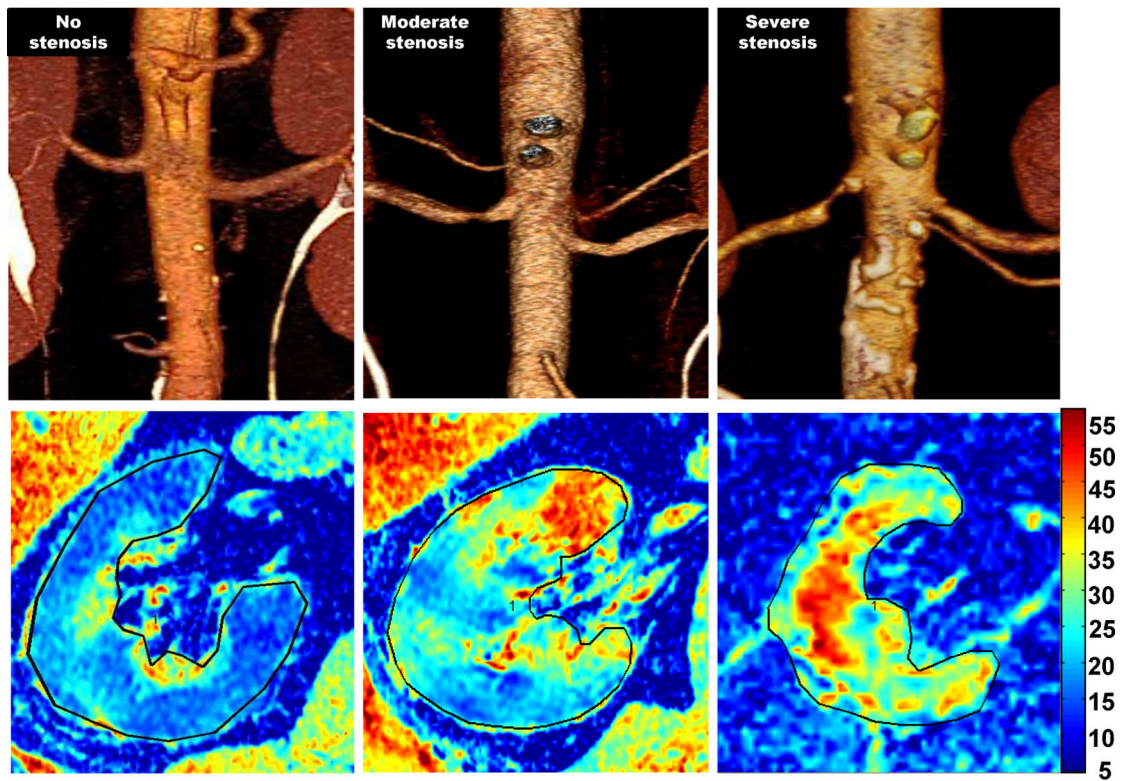
Figure-1.
CT angiographic images (upper row) of the right kidneys illustrating three patients with 1) no renal artery stenosis 2) moderate renal artery stenosis and 3) severe renal artery stenosis. Below each in the bottom row are corresponding R2* parametric maps illustrating higher fraction of axial images with elevated deoxyhemoglobin evident with progressively more severe disease.

Table 1

Example of recent reports of BOLD MR R2* values described for cortical and medullary regions obtained at (3 Tesla) magnet strength in human subjects

Study	Year	Cortex	Medulla	Comments
Li et at. (29)	2004	21.8	37.4	Healthy volunteers
Tumkur et al. (30)	2006	14.5	30.3	Baseline normal
Pruijm et al. (31)	2010	18.2	28.1	Normal, Low NA
Pruijm et al. (31)	2010	17.8	31.3	Normal, High NA
Gloviczki et al. (9)	2011	17.8	36.8	Essential Hypertension, 150 mEq NA
Gloviczki et al. (9)	2011	15.7	37.8	Moderate ARAS
Gloviczki et al. (9)	2011	21.6	39.1	Severe ARAS
Xin-Long et al. (32)	2012	18.79	25.07	CKD
Pruijm et al. (22)	2012	17.9	28.7	Type 2 diabetic patients
Vivier et al. (11)	2013	16.8-17.5	27.9-28.3	Healthy volunteers