Review

Methods of Blood Oxygen Level-Dependent Magnetic Resonance Imaging Analysis for Evaluating Renal Oxygenation

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Key Words

Blood oxygen level-dependent • Magnetic resonance imaging • Kidney • Oxygen • Hypoxia • Methods

Abstract

Blood oxygen level-dependent magnetic resonance imaging (BOLD MRI) has recently been utilized as a noninvasive tool for evaluating renal oxygenation. Several methods have been proposed for analyzing BOLD images. Regional ROI selection is the earliest and most widely used method for BOLD analysis. In the last 20 years, many investigators have used this method to evaluate cortical and medullary oxygenation in patients with ischemic nephropathy, hypertensive nephropathy, diabetic nephropathy, chronic kidney disease (CKD), acute kidney injury and renal allograft rejection. However, clinical trials of BOLD MRI using regional ROI selection revealed that it was difficult to distinguish the renal cortico-medullary zones with this method, and that it was susceptible to observer variability. To overcome these deficiencies, several new methods were proposed for analyzing BOLD images, including the compartmental approach, fractional hypoxia method, concentric objects (CO) method and twelve-layer concentric objects (TLCO) method. The compartmental approach provides an algorithm to judge whether the pixel belongs to the cortex or medulla. Fractional kidney hypoxia, measured by using BOLD MRI, was negatively correlated with renal blood flow, tissue perfusion and glomerular filtration rate (GFR) in patients with atherosclerotic renal artery stenosis. The CO method divides the renal parenchyma into six or twelve layers of thickness in each coronal slice of BOLD images and provides a R2* radial profile curve. The slope of the R2* curve associated positively with eGFR in CKD patients. Indeed, each method invariably has advantages and disadvantages, and there is generally no consensus method so far. Undoubtedly, analytic approaches for BOLD MRI with better reproducibility would assist clinicians in monitoring the degree of kidney hypoxia and thus facilitating timely reversal of tissue hypoxia.

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Introduction

Physiologically, renal tissue works under relative hypoxic conditions, particularly in the deep areas of the medulla. Constant oxygen depletion, microvasculature compromise and inflammation within the renal cortical and medullary zones make the renal parenchyma particularly vulnerable to hypoperfusion and hypoxic injury, leading to interstitial fibrosis and a vicious cycle that ultimately accelerates the progression of kidney disease [1-6]. Considering these factors, it is necessary to determine the degree of renal hypoxia in patients accurately and noninvasively, although many currently established approaches are not used to assess renal tissue oxygenation *in vivo* because they are invasive.

Blood oxygen level-dependent magnetic resonance imaging (BOLD MRI) is a noninvasive, versatile, safe and reliable technique for evaluating renal tissue oxygenation without exposure to radiation or exogenous contrast agents [7-10], and so this examination can be repeated several times without concern about side effects. It also has a high spatial resolution, making it possible to detect functional changes that have had occurred before the pathological damage of renal tissue and to reflect kidney oxygenation quantitatively. The correlation between signal strength of BOLD MRI and oxygen content of renal tissue was confirmed by direct measurement of oxygen partial pressure with oxygen-sensitive microelectrodes [11-13].

The principle of BOLD MRI is based on the physiology and strong paramagnetic properties of deoxyhemoglobin. Deoxyhemoglobin can cause uneven magnetic field around the regional kidney tissue and shorten the apparent spin relaxation time ($T2^*$) by changing the spin characteristics of the surrounding water molecules. The apparent relaxation rate ($R2^*$) is the inverse of the characteristic $T2^*$ relaxation time ($R2^*=1/T2^*$), which reflects the tissue deoxyhemoglobin level. As stated previously, $R2^*$ is positively correlated with the level of deoxyhemoglobin [14-16]. A higher $R2^*$ value in response to hypoxia corresponds to a higher tissue content of deoxyhemoglobin with lower tissue oxygenation, and vice versa. Conventionally, cortical $R2^*$ is low, with a gradient increase in $R2^*$ values from the cortex to the medulla. The highest $R2^*$ value can be recognized in the inner medullary zones, consistent with the established relative hypoxia of this region [17].

Over the last two decades, BOLD MRI has been widely used to assess changes in renal oxygen level in various kidney disease conditions, for instance, ischemic [18], hypertensive [19], diabetic [20-23] and contrast [24-26] nephropathies as well as nephrotic syndrome [27], lupus nephritis [28, 29], chronic kidney disease [30-32], acute kidney injury [33, 34] and renal allograft rejection [35-39]. It is interesting to note that BOLD MRI studies with many analytical methods in patients with different etiologies have shown inconsistent and contradictory results, reporting higher or lower $R2^*$ values.

For a better analysis of BOLD images, it has already been verified that increasing magnetic field intensity from 1.5 to 3.0 T demonstrates larger $R2^*$ variation and effectively improves the sensitivity and reliability of BOLD [40-42]. Regarding *in vivo* experiments, the kidney alignment for BOLD renal imaging (KALIBRI) algorithm was recommended to operate three-dimensional (3D) rigid image registration instead of two-dimensional (2D) time-resolved renal BOLD MRI, allowing for consistent $R2^*$ detection during breath-holds [43].

Nevertheless, finding a valid and accurate imaging analytical approach that adequately reflects renal tissue oxygenation remains a challenge. This review summarizes current methods applied to BOLD MRI analysis and their advantages and disadvantages (Table 1).

Table 1. Comparison of BOLD MRI analysis methods. BOLD MRI, blood oxygen level-dependent magnetic resonance imaging; ROI, regions of interest

Method	Advantage	Disadvantage
Regional ROI selection (1)	Initial and classical method	Manual ROI selection: 1) difficult to draw ROIs in appropriate size and location; 2) difficult to distinguish cortico-medullary zones.
Compartmental approach	No manual ROIs selection	A model: 1) insensitive to abdominal artifacts; 2) difficult to distinguish cortico-medullary zones.
Fractional kidney hypoxia	Compared with (1): simpler with lower observer variability	R2* values above 30 sec ⁻¹ are not applicable to all magnetic field strengths and other renal disease.
Concentric objects	Semi-automated method: excellent reproducibility and lower observer variability	Six layers: does not allow acquisition of sequential changes in R2* values.
Twelve-layer concentric objects	Automated method: more sensitive to evidence of small R2* changes in successive layers and lower observer variability	Twelve-layers: does not ascertain whether this is the best number layers to reflect sequential R2* changes between layers.

BOLD MRI analysis Methods

Regional ROI selection

In initial clinical studies, cortical and medullary R2* values were predominantly evaluated separately. Typically, 5-8 mm thick T2*-weighted images of sagittal or coronal slices were acquired during breath-hold with a 1.5 or 3.0 T system and the clearest image was selected with optimal contrast between cortex and medulla. Several regions of interest (ROIs) were then draw within small regions (two or three cortical and medullary ROIs, respectively) through the renal hilum (Fig. 1A). Thus, the mean R2* value for the cortex and medulla of each slice is determined.

This ROIs technique was the earliest classical analytic approach and is still commonly used today. Data from Gloviczki et al. [44] indicate that cortical and medullary oxygenation, as expressed by the R2* values, did not differ in post-stenotic kidneys as compared with contralateral kidneys or kidneys in essential hypertension. The main reason being that oxygen consumption and energy requirements for sodium transport are decreased despite the reduced blood flow and kidney volume in patients with renal artery stenosis. Recent clinical studies showed that average cortical and medullary R2* values are similar in controls, in both hypertensive and CKD patients [45, 46]. Michaely et al. [47] found no correlation between renal tissue oxygenation and estimated glomerular filtration rate (eGFR) or different stages of CKD. Most importantly, these results are inconsistent with other studies involving the ROIs method [48-50] and other analysis methods to be introduced later. This could be because the subjects enrolled in these studies had different disease states, medications, and other physiological mechanisms that may affect the R2* values in BOLD MRI.

The ROI selection has obvious shortcomings that limit its clinical application. On the one hand, ROIs of different sizes manually placed in the cortex and the medulla may affect the accuracy and reproducibility of R2* values. In other words, R2* values are susceptible to observer variability. On the other hand, it is difficult to distinguish renal cortico-medullary zones. Researchers need to draw the ROIs carefully to make their size as similar as possible and reduce the overlap between the cortex and the medulla. Under these circumstances, some nephrologists have replaced circular ROIs with rectangular ROIs containing both the cortex and the medulla to prevent R2* value variation [28]. However, it is not clear whether

Fig. 1. Two BOLD MRI analysis methods. A) Regional ROI selection: small ROIs are drawn within the cortex (ROIs 1-3) and the medulla (ROIs 4-6) to evaluate cortical and medullary oxygenation, respectively. B) Fractional kidney hypoxia method: the whole kidney zones are drawn including the cortex and medulla to fully assess kidney oxygenation. C) Fractional kidney hypoxia method: ROI is drawn containing a wide cortical area to assess cortical oxygenation.

the $R2^*$ values obtained by this method are reliable and accurate. Considering the above factors, we do not recommend that researchers analyze BOLD images using the regional ROI selection.

Compartmental approach

In general, $T2^*$ -weighted MRI images cannot clearly distinguish between the renal cortex and medulla. Small ROIs can be influenced by fluctuations caused by spatial and temporal heterogeneity in renal oxygen distribution, especially in the medulla, even though they are similar in volume [51].

Ebrahimi et al. [52] developed a model to mitigate this challenge, called the compartmental approach, assuming that the cortical and medullary $R2^*$ populations fit Gaussian and Gamma distribution, respectively. This new compartmental approach separates the $R2^*$ values into two renal compartments (excluding the collecting system, blood vessels, artifacts and cysts) and calculates the mean $R2^*$ value for each compartment. Then, it provides distribution curves and affords $R2^*$ distribution patterns within these compartments. Based on the distribution of $R2^*$ values, this method is independent of orientation and volume change, providing an algorithm to judge whether the pixel belongs to the cortex or medulla.

In recent years, Vink et al. [53] used this method to investigate the effect of renal denervation (RDN) on kidney oxygenation in patients with hypertension. They found no significant changes in renal oxygenation, possibly due to unchanged renal perfusion after RDN and small changes in cortical oxygenation “ignored” by the BOLD MRI procedure, as well as failed RDN procedure in some patients. Moreover, a recent study [54] applied a semi-automated, anatomically unbiased approach, complementary to the compartmental method, to analyze BOLD MRI images. In rats, k-means clustering segregates the whole kidney into two compartments and obviates the need for manual selection of small ROIs. The clustering analysis method shows low $R2^*$ clusters localized to the cortex, while the outer medulla demonstrates a higher $R2^*$ cluster.

Compared with the manual ROIs method, the relaxivity index $R2^*$ obtained using the compartmental approach shows less variability and operator dependency, with improved time-efficiency and reproducibility. Because there is no need for manual ROIs selection, the distribution function-based approach breaks the inherent limitations of choosing ROIs of appropriate size and location. However, it depends on the heterogeneity of medullary oxygenation and is insensitive to the abdominal susceptibility artifact, which must be manually excluded in the analysis. The boundaries between the cortex and medulla may be blurred when the oxygenation of the medulla is approximate to that of the cortex. To date, it is still uncertain whether this method is reliable under different conditions and in other models.

Fractional kidney hypoxia method

Recently, fractional kidney hypoxia was introduced for identifying oxygenation within the renal parenchyma. The large ROI obtained using a freehand tool traces the entire kidney zones encompassing both cortex and medulla, determined by measuring the percentage of the entire axial image section with $R2^*$ values above a certain threshold (usually $>30 \text{ sec}^{-1}$) (Fig. 1B). In addition, the ROI of the wide cortical area excluding the renal collecting system, cysts, calculus and hilar vessels was placed so as to evaluate cortical oxygenation (Fig. 1C). As described by Saad et al. [55], fractional hypoxia was negatively correlated with renal blood flow, tissue perfusion and GFR compared with regionally selected cortical and medullary segments.

A combination of renal parenchyma and large cortical ROI assessment provides a sensitive and objective method for analyzing renal BOLD MRI data [56]. It has a higher inter-rater agreement than the traditional ROIs method, and greatly simplifies image analysis. Because of the full use of all available slices, fractional kidney hypoxia can marginally reduce the bias resulting from operator selection of ROIs.

Larger ROIs that include the entire kidney may provide more valid and reliable mean $R2^*$ values, but often contain cortico-medullary overlap zones as well as the deepest most hypoxic sections of the medulla [51]. This method of analysis also could not solve the inherent sampling problem owing to it only sampling one part of the kidney. Furthermore, it might be argued that the choice of $R2^*$ values above 30 sec^{-1} as the threshold of hypoxia was arbitrary and could not be applied to different magnetic field strengths and other renal disease. To gain more flexibility in future studies, it is requisite to select the threshold relative to the mean cortical $R2^*$ or the cortical and medullary $R2^*$ ratio [57].

Concentric objects method

Recent publications proposed a new semi-automated “concentric objects” (CO) method (or “onion peel” method) for analyzing BOLD images. Corresponding $R2^*$ maps were acquired with four coronal slices and then the renal parenchyma was semi-automatically divided into six layers of equal thickness by the program. The investigators then sketched the contours of the outer (cortical side) and inner (medullary side) border of the renal parenchyma manually and reported the $R2^*$ values of all six layers. The layers comprised the cortex, medulla, or a combination of both. When repeating the examination, layers can be traced at the same depth. Studies performed by Piskunowicz et al. [58] showed that the CO method, compared with the classical ROIs method, showed excellent reproducibility and lower inter-observer variability in all tested layers of the kidney in both non-CKD and CKD groups.

Nevertheless, the CO method must be applied to oval-shaped kidneys. In addition, blood vessels, cysts, tumors, artifacts and the urine-containing renal pelvis are difficult to be excluded. The relatively limited number of layers hinders the acquisition of sequential changes in $R2^*$ values. Therefore, this technique is devoid of precision although it can reduce operator bias considerably. Further clinical and animal experiments are necessary to evaluate the exact quantity of cortical and medullary areas per layer with this method.

Twelve-layer concentric objects method

To overcome the limitations inherent in the CO method, Milani et al. [59] developed the twelve-layer concentric objects (TLCO) method based on the CO method. The TLCO method divides the renal parenchyma into twelve layers of equal thickness in each coronal slice by using a locally automated procedure. Investigators evaluated the concentric objects in three dimensions. The collection of four voxels at a constant depth in the renal parenchyma were designated CO3D. So, there are four slices, twelve layers in each slice, and twelve CO3D within each kidney, in this method.

This automated technique successfully provides a means for monitoring the mean $R2^*$ value of each layer by obtaining the average of the $R2^*$ values in each of the twelve CO3Ds. Instead of absolute $R2^*$ values, a $R2^*$ radial profile curve is drawn, defining the percent of equal relative depth (ranging from 0% to 100%) as the x-axis and the mean $R2^*$ of each CO3D as the y-axis. The $R2^*$ changes in successive layers from superficial to deeper renal tissue was obtained by calculating the steepness of the relevant curve. From this study, the $R2^*$ value increased significantly in the outer layers and the largest change in $R2^*$ is seen in the deeper layers, suggesting lower kidney oxygenation, more pronounced in the medulla. The slope of the $R2^*$ curve associated positively with eGFR in CKD patients, which means that the higher the eGFR of patients, the steeper the corresponding $R2^*$ slope.

This optimal TLCO method is independent of observer-selection and focuses more on intra-compartmental distribution rather than mean $R2^*$ values. It makes full use of the geometry of the whole renal parenchyma and provides detailed layer-by-layer information, making it more sensitive to small changes in $R2^*$ values. Briefly, compared with the classical ROIs and CO methods, the TLCO method improves the accuracy of distinguishing the cortex and medulla of the kidney and is more sensitive to evidence of small changes in renal $R2^*$ values during administration of renin inhibitors and diuretics [60].

Although, the $R2^*$ slope was selected as a marker of cortico-medullary differentiation, it still directly depends on the observer's manual choice of the inner profile of the renal parenchyma. Nevertheless, compared with the CO method, the TLCO technique has twice the number of layers, however, whether twelve layers is most appropriate to accurately reflect the difference between layers and the sequent $R2^*$ changes is uncertain. Thus, more investigation is needed to demonstrate how many onion peel-like layers are most suitable for this method.

Limitations and Future Directions

It is a prerequisite that BOLD MRI analysis reflects tissue oxygenation and that tissue and blood oxygen levels are in equilibrium. However, some studies have indeed demonstrated that kidney vascular oxygenation and tissue oxygenation may actually vary [61, 62].

As a result of the strong positive magnetic susceptibility of deoxyhemoglobin, the $R2^*$ value is easily affected. Additionally, several factors other than deoxyhemoglobin also can influence $R2^*$ values, such as hydration status, renal blood flow, blood PH, hematocrit, sodium intake, susceptibility effects and vascular volume [50, 63-67]. Some investigators suggest that spatial distribution of local static magnetic field heterogeneity and susceptible abdominal artifacts due to respiratory and air-filled colonic loop movement largely limit the clinical application of BOLD MRI. Intake of drugs by patients before BOLD MRI examination, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers [68-71], beta blockers [72] or diuretics [45, 73-75], could confound the use of BOLD MRI in measuring renal oxygenation as a result of increasing oxygen delivery and reducing oxygen consumption. Nonetheless, it is indeed challenging to remove and eliminate the effects of all drugs that affect renal oxygenation particularly in subjects in need of blood pressure control in the clinical setting.

The main shortcoming of all currently available BOLD MRI analysis methods is the absence of cortico-medullary differentiation, resulting in difficulties in manual tracing of appropriate ROIs. The aforementioned study by Milani et al. [59] supports the concept of BOLD MRI combined with blood flow-based MRI techniques, such as arterial spin labelling, which may potentially help to distinguish the cortico-medullary zones in the future.

The apparent diffusion coefficient (ADC) in diffusion weighted MRI (DW-MRI) offers a non-invasive way to quantify renal fibrosis and microcirculation [49, 63, 76-78]. It has previously been shown that reduction in ADC is demonstrably related to degree of fibrosis, CKD and lupus staging [79-81]. BOLD MRI combined with DW-MRI, are capable of early identifying decline of renal function, however, further investigation is still required.

Conclusion

Numerous techniques have been used to analyze BOLD MRI, but there is still no unified standard method so far. The disadvantages mentioned above limit its clinical application. We believe that further exploration of new methods of BOLD MRI analysis will improve evaluation sensitivity. BOLD MRI can detect changes in intra-renal oxygen metabolism before any irreversible damage occurs in the renal parenchyma and interstitium.

Disclosure Statement

The authors of this manuscript state that they do not have any Disclosure Statements.

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