Blood Oxygen Level–Dependent (BOLD) MRI in Renovascular Hypertension

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Abstract

Establishing whether large vessel occlusive disease threatens tissue oxygenation and viability in the post-stenotic kidney is difficult for clinicians. Development of blood oxygen level–dependent (BOLD) MRI methods can allow functional evaluation of regional differences in deoxyhemoglobin levels within the kidney without requiring contrast. The complex renal circulation normally provides a gradient of oxygenation from a highly vascular cortex to much reduced levels in the deep sections of medulla, dependent upon adjustments in renal afferent arterioles, oxygen consumption related to solute transport, and arteriovenous shunting related to the juxtaposition of descending and ascending vasa recta. Studies with BOLD imaging have identified adaptation to substantial reductions in renal blood flow, volume, and glomerular filtration rate in post-stenotic kidneys that preserves medullary and cortical oxygenation during medical therapy. However, extreme vascular compromise overwhelms these adaptive changes and leads to cortical hypoxia and microvascular injury.

Keywords

Renal artery stenosis; Renovascular hypertension; Oxygen; BOLD MRI; Magnetic resonance imaging; Hypoxia; Kidney; Oxidative stress; Ischemic nephropathy

Introduction

Evaluation of renovascular disease, particularly atherosclerotic renal artery stenosis (ARAS), presents daunting challenges for clinicians dealing with secondary hypertension. The prevalence of ARAS is increasing in developed countries, along with aging of the population. When imaging of the renal arteries is included in vascular studies for conditions associated with atherosclerosis, including coronary and peripheral vascular disease, some degree of renal artery stenosis can be identified in 18% to 30% or more of patients [1•]. Remarkable advances in antihypertensive drug therapy, particularly agents that block the renin-angiotensin system, have made it possible to achieve satisfactory blood pressure control for many of these patients and have improved cardiovascular outcomes as compared

with treatment not using these agents [2]. As a result, clinical treatment algorithms are controversial, especially in the light of recent publications from clinical trials such the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial [3••] and the STAR study of stent placement in patients with ARAS [4], which question the added benefit of revascularization in ARAS [5].

Determining when occlusive vascular lesions actually threaten the oxygenation and viability of the affected kidney remains an elusive goal, in part because glomerular filtration function normally is associated with a vast oversupply of the blood required for metabolic activity [6]. Paradoxically, the complex anatomy of renal vessels and heterogeneous oxygen consumption within the cortical and medullary regions are recognized to leave some areas, particularly within the deep medulla, at the brink of hypoxia much of the time. Powerful tomographic magnetic resonance tools such as blood oxygen level–dependent (BOLD) MRI, which provide an estimate of in vivo tissue oxygenation, represent an important advance in understanding the pathophysiology of renovascular disease. This review summarizes our current understanding of the use of BOLD MRI as it applies to renovascular hypertension.

Blood Flow and Oxygenation Within the Kidney

The renal circulations and distribution of blood flow are complex. Because renal blood flow is unusually high compared with that of other organs, relative "hyperoxia" and its potential for oxidative free-radical formation is a genuine threat [7••]. As a result, tissue oxygen levels are regulated by a triad of pathways specific to the kidney, namely alterations in afferent arteriolar blood flow, oxygen consumption (primarily governed by tubular solute transport), and arteriovenous shunting related to the apposition of descending and ascending vasa recta [8•]. Studies of microcirculatory regulation indicate that admixture of arterial and venous deoxygenated venous blood in mammalian kidneys produces relatively constant cortical oxygen tension, in the range of 50 mm Hg [8•]. Renal blood flow and pressure show little change until the renal artery lumen cross-sectional area falls by 70% to 80% [9]. When a "critical" degree of stenosis is attained, renal hypoperfusion leads to a cascade of events from initial activation of the renin-angiotensin system to the rarefaction of small renal vessels, kidney fibrosis, loss of function, and atrophy [9]. Renal changes may be reversible up to a certain point, beyond which even technically perfect revascularization often does not restore renal function. No studies have yet completely characterized the nature and duration of the structural alterations that render kidney function unsalvageable.

Tissue damage within the kidney resulting from decreased renal blood flow may differ between locations, possibly because renal structures differ in their vulnerability, on account of heterogeneous basal oxygenation and metabolic activity. Local differences of blood supply and energy-dependent transport produce major differences in oxygen tension between the cortex and inner medullary regions. Furthermore, local differences in oxygen supply and tubular transport activity result in substantial spatial heterogeneity even within the medulla (Fig. 1, *bottom*). The cortical microcirculation receives a vast surplus of oxygenated blood. Even with substantial reduction of blood flow, cortical tissue has enough oxygen for the metabolic demands. Studies of oxygen delivery and consumption in anesthetized rabbits indicate that acutely reduced filtration and oxygen consumption can

leave tissue oxygen levels stable even if cortical blood flow is reduced by up to 40% [10, 11]. A smaller portion of blood flow is delivered to deeper medullary regions of the kidney via post-glomerular vasa recta; in these regions, active metabolic processes dependent upon aerobic energy pathways lead to oxygen consumption and local areas of hypoxia, even within normal kidneys. Local gradients of cortical and medullary oxygenation are closely regulated, sometimes independently from each other. Remarkably, these regions can tolerate reduced blood flow with compensatory changes by numerous vasoactive systems within the circulation. In a rat model, for example, angiotensin II infusion produced a 40% decrease of cortical perfusion, but medullary perfusion was unchanged, apparently protected by prostaglandin E2 synthesis [12]. Quantitative changes in the degree of arteriovenous shunting as a result of changes in renal blood flow appear to maintain the oxygen tension and adjust local areas of blood supply, but also may render some focal regions more susceptible to hypoxia [10].

Much of medullary oxygen consumption is determined by solute transport. Cortical O_2 levels in anesthetized swine models, for example, average 40 to 50 mm Hg, as measured by tissue oxygen probes (Table 1). Medullary O_2 tension in normal animals under the same conditions average 20 to 23 mm Hg but rise to 41 mm Hg after the administration of furosemide, consistent with its action inhibiting solute transport in the Loop of Henle [13••, 14]. Blood returning from hypoxic regions travels adjacent to descending vasa recta with higher oxygen levels. When combined with some degree of arteriovenous mixing from preglomerular shunts, renal venous oxygen returns to inflow levels, sometimes above efferent arteriolar oxygen levels within the cortex [7••]. These characteristics have made it difficult to establish valid estimates for tissue oxygenation within disparate regions of the kidney in the intact organism.

BOLD MRI Applied to the Kidney

MRI allows functional imaging of individual regions of interest within the kidney parenchyma. BOLD imaging takes advantage of the paramagnetic properties of deoxyhemoglobin to generate images whose signal intensity reflects tissue O_2. Deoxyhemoglobin generates local magnetic-field inhomogeneities leading to more rapid spin dephasing and a corresponding increase in "relaxivity," defined as R2*. Oxygenated hemoglobin is diamagnetic and is devoid of these properties. The amount of deoxyhemoglobin functions as a biologic "contrast agent" and can be related to the strength of R2*-weighted pulse sequences. Studies comparing 1.5 and 3.0 Tesla magnetic fields in humans indicate that higher magnetic field strength increases the measurable R2* levels within deoxygenated regions of interest (ROIs), particularly in the medulla [15].

A set of parametric images of R2* is generated from the BOLD sequence data by fitting signal intensity data from each echo on a voxel-by-voxel basis to an exponential function describing the expected signal decay as a function of echo time (TE) and solving for the unknown value of R2*. Parametric maps of R2* over the image illustrate the R2* translation of renal structures. Typically, cortex can be identified by lower R2* values, with a gradient developing to higher R2* levels in the deeper medullary sections (Fig. 1). Parametric imaging makes the selection of ROIs more focused, especially when the deeper parts of the

medulla are targeted, and allows the exclusion of adjacent artifacts from areas outside the kidneys. However, variable oxygenation within the kidney makes interpretation of BOLD MRI for specific regions difficult. The selection of ROIs using T2*-weighted gradient echo images sometimes depicts more gradual demarcation of deoxyhemoglobin than can be identified using iodinated contrast. The importance of reliably remaining within cortex and/or medulla for serial measurements highlights the importance of limiting the ROI to well-delineated, small segments in cortex and medulla, as we have proposed [15]. On the other hand, the use of parametric maps may direct ROI selection to areas with the most extreme hypoxia, under-sampling regions within the heterogeneous medulla that are better oxygenated (Fig. 1).

Placement of oxygen-sensing electrodes in experimental animals at various locations within the kidney confirms that tissue oxygen levels indeed follow the pattern of oxygenation gradients observed with BOLD MRI. Average levels of tissue oxygen tension in the mammalian kidney range from about 50 mm Hg in cortex to as low as 15 to 20 mm Hg in the deep sections of the medulla. These levels coincide with a range of hemoglobin oxygen saturation, which falls steeply from 85% to 15%, thereby making this a range favorable for detection using BOLD imaging. Results from experimental studies in rats [16••, 17] and other models [18, 19] using oxygen probes confirm that tissue oxygen levels fall by 45% to 50% in moving from cortex to deep medullary regions.

Examples of rapid changes of tissue oxygenation detectable using BOLD imaging include inhibition of solute transport with diuretics [13••] and prostaglandin inhibition, reduction in blood flow during acute vascular occlusion [19, 20], and models of ureteral obstruction [18]. Many of these studies suggest that alterations in oxygen consumption, rather than changes in blood flow, primarily determine medullary R2* levels. However, studies of local blood flow reduction using inhibitors of nitric oxide synthase in animals and humans illustrate that even small adjustments in blood flow have the potential to raise medullary R2* [16••]. Signal strength for T2* (the reciprocal of R2*) can be affected by other local factors influencing the homogeneity of magnetic dipole alignment, including the volume of tissue and blood (i.e., hemoglobin concentration) contained in a measured volume. Some authors question whether changes in deoxyhemoglobin precisely reflect tissue oxygenation status under all conditions [21].

Study of different oxygenation zones is of clinical relevance [6]. BOLD MRI studies in humans using 1.5 Tesla systems identified the potential to detect alterations within medulla and cortex after administration of nephrotoxic contrast [22], allograft injury [23], water loading, and occlusive renal arterial disease [24, 25••]. Several of these have been assumed to induce local "ischemia" related to reduced blood flow. Remarkably, conditions that also severely limit tubular metabolic activity, such as acute interstitial inflammation associated with transplant rejection, acute tubular necrosis, or even nonfunctioning renal atrophy beyond an occluded vessel, are associated with reduced oxygen consumption. Measured R2* levels (and thus deoxyhemoglobin) are low in these settings.

Acute Changes in Oxygenation

Serial studies in acute experimental models demonstrate a progressive rise in R2* in both cortex and medulla after stepwise reductions in renal blood flow when the kidney is otherwise functional [20]. Animal studies in a swine model show regional decreases in renal oxygenation during graded ARAS that also appear as changes in R2* signal under similar conditions [19]. Temporary renal artery occlusion in rats induces changes in medullary blood flow and reduction in R2* that persist 3 days after the event [26].

Important maneuvers that extend the utility of BOLD MRI include the use of measures that change renal solute transport and oxygenation, such as a water load or the use of diuretics. For example, increasing solute transport by increasing sodium intake in individuals with normal kidney function leads to a rise in oxygen consumption, thereby raising R2* [27••]. Therefore, beyond assessment of basal intrarenal oxygenation levels as reflected in R2*, the use of a functional challenge can provide insight regarding oxygen consumption related to tubular action. Not surprisingly, changes in R2* observed after administering furosemide are blunted in conditions associated with chronic and marked changes in renal function and structure [25••]. This simple maneuver may be useful to assess the viability of the kidney tissue without depending upon the absolute baseline level of R2*.

Can BOLD MRI Be Applied to Renovascular Disease and "Ischemic Nephropathy" in Humans?

Many experimental models of renovascular occlusion have identified a broad array of mechanisms associated with renovascular disease. These include activation of the renin-angiotensin-aldosterone system and numerous other pathways, including oxidative stress, sympatho-adrenergic activation, microvascular rarefaction, and inflammation [28]. As a rule, vascular occlusive disease develops slowly, unlike many experimental models that have used "clip hypertension." Many of the pressor pathways can become activated at different times in the development of sustained hypertension and progressive vascular compromise [29•]. Rarely is the exact onset of critical renovascular disease known. Whether reductions in renal perfusion pressure truly induce hypoxia within the kidney parenchyma under these conditions has not been elucidated.

To examine tissue oxygenation in human atherosclerotic disease, our group studied individuals with unilateral ARAS using 3.0 Tesla BOLD MRI under carefully controlled conditions with a known, constant sodium intake of 150 mEq per day [25••]. Individual kidney blood flows within both the cortex and medulla were measured using contrast transit time and regional volumes measured by multidetector CT (MDCT). Initial studies were performed in patients with a reasonably preserved glomerular filtration rate (GFR) and serum creatinine less than 1.7 mg/dL and who otherwise met the entry criteria for the Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL) trial [5]. These individuals were compared with age-matched patients with essential hypertension undergoing the same protocol. All were taking agents that blocked the renin-angiotensin system. These studies confirmed that high-grade ARAS sufficient to activate the renin-angiotensin system does lead to decreases in kidney size and blood flow, as well as GFR in

the affected kidney. Surprisingly, average levels of cortical and medullary R2* in these ARAS patients did not differ from those of the patients with essential hypertension or from those of the contralateral, normally perfused kidney (Table 2) [25••]. Despite major reductions in blood flow in the stenotic kidneys sufficient to elevate levels of plasma renin activity, levels of R2* were similar to those in the other patients, indicating preservation of the cortical and medullary oxygenation in these patients with preserved kidney function treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. The response to furosemide administration of medullary R2* in the stenotic kidney was blunted, however, compared with the contralateral kidneys, suggesting that oxygen consumption in the stenotic kidney was less a function of solute transport than it was in the contralateral kidney under these conditions. In fact, it is likely that the contralateral kidney increases its metabolic activity as it assumes some of the filtration and reabsorption functions of the stenotic kidney. We interpret these data to indicate a remarkable intrarenal adaptation in the stenotic kidney that effectively preserves oxygenation balance between cortex and medulla despite reduced blood flow and GFR. One explanation is that the fall in GFR reduces solute filtration, thereby reducing the "workload" and metabolic energy requirements in deeper medullary tissues. Our results are consistent with similar findings in a chronic rat model of mild renovascular hypertension, which demonstrated no evident drop-off in "downstream" renal oxygen content as measured by BOLD MRI using 7.0 Tesla magnetic field strength [30]. These observations indicate that differences between acute and chronic vascular compromise reflect compensatory alterations that circumvent true tissue hypoxia for many patients with chronic conditions. Our results provide one explanation for the clinical trial data indicating that patients with ARAS often can be treated using medical therapy alone for many years without worsening renal function [5].

The capacity for circulatory adaptation within the kidney obviously has limits, however. We recently extended our human studies using MDCT and BOLD MRI to patients with more advanced reductions in blood flow, associated with duplex ultrasound above 384 cm/sec and severe cortical atrophy. In these cases, both kidney volume and tissue perfusion in the cortical regions were reduced. Levels of cortical R2* were elevated in this group, suggesting that overt tissue hypoxia was developing. Deep medullary regions continued to have high R2* levels that did not differ from those in otherwise normal kidneys. The extent of medullary tissue with elevated R2* levels was considerably wider, however. These observations are supported by studies using other estimates of cortical perfusion and dimensions [19]. In patients like these, the capacity for changes in volume and filtration to compensate for reduced blood flow appear to have been overwhelmed, leading to cortical hypoxia. These data agree closely with other studies indicating that loss of cortical thickness is a marker of more severe occlusive disease [31•]. Our results demonstrate for the first time that significant kidney damage in humans with ARAS is characterized by localized hypoxia in vivo. Preliminary data using transvenous biopsies from stenotic kidneys indicate that the degree of tissue injury is closely related to the severity of blood flow decrements in such patients [32].

The mechanisms underlying the development of genuine hypoxia in severely damaged kidneys appear to be the loss of intrarenal vessels and the development of scarring. Experimental studies in a swine model of ARAS indicate that extensive reductions in renal

blood flow eventually produce microvascular rarefaction in the post-stenotic kidney that is associated with the loss of renal function [33]. These changes produce major disturbances in local cytokines, activation of inflammatory pathways within the affected kidney, and eventual parenchymal fibrosis—changes that are accelerated by an atherogenic milieu. Importantly, studies in the swine model demonstrate that restoration of vascular patency alone does not reverse the process of fibrogenesis [34••, 35], an observation that is substantiated by similar observations in series of human patients treated with renal revascularization. Recent studies from our laboratory and others suggest that implementation of other (or adjunctive) measures such as infusion of endothelial progenitor cells may facilitate repair or prevention of renal parenchymal injury [36••].

Conclusions

How do these data mesh with clinical evaluation of patients with ARAS? We propose that BOLD MRI may provide major improvements in two domains: (1) BOLD studies can identify individuals for whom an observed vascular occlusion has not produced major disruption of tissue oxygenation or specific disruption of cortical to medullary oxygenation gradients. This finding may support ongoing management without apparent risk of "hypoxic" injury, or at least may indicate that the post-stenotic kidney is well preserved from an oxygenation perspective. (2) A kidney in which BOLD imaging demonstrates cortical hypoxia and/or widening medullary regions of hypoxia likely is at risk for additional tissue injury. We propose using the results of BOLD MRI as real-time markers of local blood flow and oxygenation reserve, to more rationally identify individuals who may truly benefit from renal revascularization and/or adjunctive maneuvers to repair kidneys that are at imminent risk of demise.

It is premature to indicate that these goals will be met. Our interest in the development of improved tools to identify kidneys at risk from vascular injury coincides with recent trials that challenge the widespread benefit of renal revascularization. We believe that one outcome of these ambiguous trials will be a tendency to investigate fewer patients early in the course of renovascular disease, leading to the likely appearance in the future of more patients with vascular occlusion that is much further established. Experienced clinicians already encounter patients in whom total renal occlusion has rendered one kidney—and sometimes both kidneys—beyond salvage. We hope that further studies using tools such as BOLD MRI will allow more precise identification of patients before irreversible kidney injury occurs.

Acknowledgments

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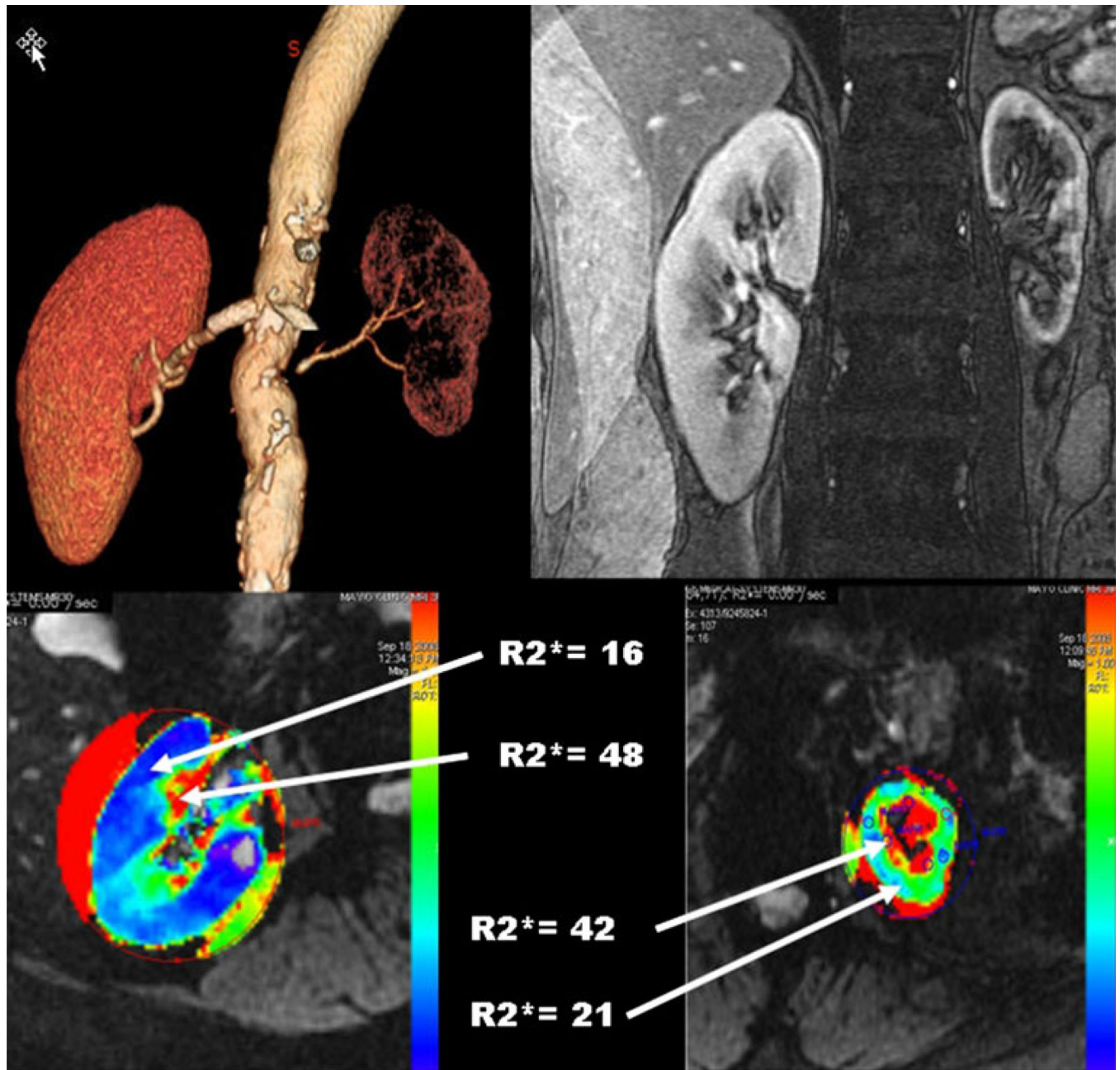
Fig. 1.
CT angiogram (*upper left*) showing preserved blood flow to the right kidney and advanced occlusive disease to the left kidney. T2* imaging (*upper right*) illustrates the gradient of oxygenated blood between cortex and medullary region of both kidneys. R2* parametric maps using blood oxygen level–dependent (BOLD) MRI identifies rising R2* levels in a deep medullary region in the normal kidney (*lower left*), with a more extensive medullary region of hypoxia and elevated level of cortical R2* as well evident in the kidney with vascular occlusion (*lower right*). These measurements illustrate the limitations of the post-

stenotic kidney in adapting to reduced blood flow, eventually developing overt cortical hypoxia and widening regions of medullary deoxygenation. (*From* Textor and Lerman [9])

Table 1

Examples of direct measurement of renal tissue oxygen and recent reports of BOLD MR R2* values[a]

Study	Year	Cortex	Medulla	Species/Comments
Oxygen tension (mean O_2 pressure, *mm Hg*) measured using oxygen probes[b]				
Lubbers et. al. [38]	1997	30–49	10–25	Rat
Welch et al. [37]	2005	31–42	–	Rat
Palm et al. [17]	2008	49	–	Rat
Warner et al. [13••]	2011	44	23	Pig
BOLD MRI (3.0 T): R2* values in animal models				
Prasad et al. [39]	2010	27.1	32.3	Control mice
		31.7	43.1	Diabetic mice
BOLD MRI (3.0 T): R2* values in humans				
Li et al. [40]	2004	21.8	37.4	Healthy volunteers
Tumkur et al. [41]	2006	14.5	30.3	Baseline normals
Gloviczki et al. [25••]	2010	18.6	38.2	Essential hypertension, 150 mEq Na
Prujim et al. [27••]	2010	17.8	31.3	Normal, high Na
		17.4	30.3	Essential hypertension, high Na

[a]Though cortical values are generally comparable, medullary values are especially susceptible to differences in selection of regions of interest, in part because of greater heterogeneity within medullary regions

[b]Measured in anesthetized animals

BOLD blood oxygen level–dependent; *Na* sodium

Table 2

Kidney functional parameters in patients with essential hypertension (EH) and atherosclerotic renal artery stenosis (ARAS)

Single kidney	EH (N=28)[a,b]	ARAS Stenotic (n = 14)[a]	Contralateral (n=14)[a]
Total kidney volume (CT), *cc*	144.3±6.6	118.6±9.9[c,d]	155.4±13.7
Cortical volume, *cc*	96.1±5.9	80.1±7.8[d]	111.8±12.1
Medullary volume, *cc*	48.2±3.5	38.5±4.5	43.6±6.1
Total renal blood flow, *mL/min*	404.6±28.9	269.7±42.2[c,d]	383.7±49.0
MRI studies: BOLD magnetic resonance			
Basal cortical R2*, s^{-1}	18.6±0.6	170.0±0.6	16.9±0.5
Basal medullary R2*, s^{-1} [e]	38.2±1.0	37.5±1.5	41.9±1.4
Change in R2* after furosemide	7.0±1.1	5.7±1.8[d]	9.4±1.9
PRA, ng/mL per h	8.2±2.1	24.3±5.0[c,d]	18.3±4.3

[a] Data are mean ± SEM

[b] Data from both kidneys were compiled

[c] $P<0.05$ vs EH

[d] $P<0.05$ vs contralateral

[e] All of the values of medullary R2* were higher than cortical values ($P<0.0001$)

PRA plasma renin activity
(*From* Gloviczki et al. [25••], with permission)