Renal Relevant Radiology: Renal Functional Magnetic Resonance Imaging

Behzad Ebrahimi, Stephen C. Textor, and Lilach O. Lerman

Summary

Because of its noninvasive nature and provision of quantitative measures of a wide variety of physiologic parameters, functional magnetic resonance imaging (MRI) shows great potential for research and clinical applications. Over the past decade, application of functional MRI extended beyond detection of cerebral activity, and techniques for abdominal functional MRI evolved. Assessment of renal perfusion, glomerular filtration, interstitial diffusion, and parenchymal oxygenation turned this modality into an essential research and potentially diagnostic tool. Variations in many renal physiologic markers can be detected using functional MRI before morphologic changes become evident in anatomic magnetic resonance images. Moreover, the framework of functional MRI opened a window of opportunity to develop novel pathophysiologic markers. This article reviews applications of some well validated functional MRI techniques, including perfusion, diffusion-weighted imaging, and blood oxygen level–dependent MRI, as well as some emerging new techniques such as magnetic resonance elastography, which might evolve into clinically useful tools.

Introduction

Magnetic resonance imaging (MRI) is a powerful modality. Although functional MRI initially referred mainly to the procedure used to measure brain activity by detecting associated changes in blood flow distribution, today it encompasses a large variety of techniques measuring diverse physiologic markers in many organs. In research, higher magnetic field strengths and sophisticated pulse sequences have opened a window of opportunity to explore new physiologic processes that are detectable by MRI (Table 1). Clinically, MRI has evolved into a sensitive and accurate diagnostic tool that provides information that cannot be achieved noninvasively using other means. Computed tomography (CT) with iodinated contrast agents and renal nuclear imaging using radiolabeled isotopes can also provide renal functional assessment. Whereas CT possesses high spatial and temporal resolution, the spatial resolution of renal nuclear imaging is low and its measurements are semiquantitative. Both techniques require exogenous contrast media and exposure to ionizing radiation. On the contrary, MRI uniquely acquires detailed information without imposing ionizing radiation, and many applications do not necessitate using contrast agents. Although renal functional MRI tools are still largely experimental, understanding their inherent power may facilitate adaptation for clinical practice. Here we review some of the most useful and potentially clinically applicable renal functional MRI methods as well as their prospects for assessing renal pathology.

Renal Perfusion

Renal hemodynamic parameters are important markers of many renal pathologic conditions. Although their assessment has been more common in renovascular disease, such as renal artery stenosis, it can be useful in other pathologic conditions that affect the microvasculature, renal blood flow, vascular resistance, or permeability such as CKD, hypertension, metabolic syndrome, diabetes, and sepsis (1). Moreover, perfusion measurement may help guide kidney transplant management and treatment of renal lesions (Table 2).

Hemodynamic parameters are often derived from mathematical models, which link them to dynamic changes of MR signal intensity during transition of the contrast-enhancement agent through the tissue. Lack of a standard protocol for perfusion measurement, as well as complicated fluid dynamics in the kidney that require more elaborate analytical models than in many other organs, have restricted wide clinical application of this technique, yet it has been used in a large number of experimental basic and clinical studies. The most common magnetic resonance (MR) approaches for perfusion measurement include dynamic contrast-enhanced (DCE) and arterial spin labeling (ASL).

DCE-MRI

Hemodynamic measurements with DCE-MRI rely on exogenous tracers that affect the blood MR characteristics. A tracer bolus alters two independent MR time constants and consequently creates dynamic contrast that can be detected using $T_1$ and $T_2^*$-weighted perfusion measurements. Tissue carrying a contrast agent that shortens the $T_1$ and $T_2^*$ relaxation times appears brighter in $T_1$-weighted and darker in $T_2^*$-weighted images. MR signal intensity can be translated to contrast media concentration in order to generate a...
concentration-time curve for any region of interest (Figure 1). A concentration-time curve depicts vascular, proximal, and distal tubular phases in the cortex, whereas only vascular and tubular (Loop of Henle) phases are usually distinguishable in the medulla within the same timeframe. These curves carry important functional information about sub-compartments of the kidney and are the primary sources of data for perfusion models to calculate hemodynamic parameters. Generally, a DCE-MRI acquisition continues for 3–10 minutes after administration of the contrast bolus. Abdominal imaging artifacts, including motion artifacts perpetuated by respiration, add to the complexity of kidney perfusion measurements. Although several methods may address respiratory motion artifacts, the most

Table 1. Key terms in magnetic resonance imaging

<table>
<thead>
<tr>
<th>Term</th>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Relaxation times</td>
<td></td>
<td><strong>T</strong>&lt;sub&gt;1&lt;/sub&gt; A tissue-specific measure of the time that tissue (longitudinal) magnetization takes to restore to its equilibrium value</td>
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<td>Longitudinal relaxation time</td>
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<td>Transverse relaxation time</td>
<td><strong>T</strong>&lt;sub&gt;2&lt;/sub&gt; A tissue-specific time constant and source of contrast in magnetic resonance images which reflects the time taken for tissue (transverse) magnetization to decay by loss of coherence</td>
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<tr>
<td>T&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;* A source of magnetic resonance contrast and a measure of (transverse) magnetization decay time, including both tissue-specific mechanisms and field inhomogeneity that contribute to signal decay</td>
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<td>Weighted imaging</td>
<td></td>
<td><strong>T</strong>&lt;sub&gt;1&lt;/sub&gt;-weighted imaging A group of imaging sequences that rely on exogenous contrast or intrinsic <strong>T</strong>&lt;sub&gt;1&lt;/sub&gt;-relaxation time properties of different tissues. Images are acquired before the (longitudinal) magnetization of tissues restores to equilibrium. Therefore, tissues with shorter <strong>T</strong>&lt;sub&gt;1&lt;/sub&gt; (and faster magnetization recovery) appear bright, whereas tissues with longer <strong>T</strong>&lt;sub&gt;1&lt;/sub&gt; (and slower relaxation) remain dark</td>
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<tr>
<td>T&lt;sup&gt;*&lt;/sup&gt; (and <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;)-weighted imaging</td>
<td><strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;* Uses the differences of the <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;* (or <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;) relaxation times as the source of contrast. Regions with shorter <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;* (or <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;) exhibit a faster decay of MR signal and appear darker, whereas regions with longer relaxation time undergo a slower signal decay and therefore appear brighter. Similar to <strong>T</strong>&lt;sub&gt;1&lt;/sub&gt;-weighted imaging, the contrast can be enhanced using exogenous contrast media</td>
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<tr>
<td>Diffusion-weighted imaging</td>
<td>DWI</td>
<td>Reflects the level of restriction for water molecule free translocation in biologic tissue. DWI maps provide information about the microstructure of the tissue</td>
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<td>Perfusion-weighted imaging</td>
<td>PWI</td>
<td>In the kidney, PWI is sensitive to fluid translocation in the microvasculature and tubules, which can be enhanced using endogenous or exogenous contrast media. A quantitative map of perfusion may be generated from a set of perfusion-weighted images</td>
</tr>
<tr>
<td>Other technical terms</td>
<td></td>
<td><strong>DCE</strong> Imaging performed during the passage of exogenous contrast agents through a target tissue</td>
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<td>Dynamic contrast-enhanced imaging:</td>
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<td>Arterial spin labeling</td>
<td>ASL</td>
<td>An imaging technique to measure perfusion by acquiring a set of perfusion-weighted images using magnetically labeled inflowing blood as the contrast agent. Labeling takes place by applying a radiofrequency pulse that temporarily alters blood flow magnetization</td>
</tr>
<tr>
<td>Blood oxygen level-dependent imaging</td>
<td>BOLD</td>
<td>An imaging technique that provides information about blood oxygenation by acquiring a set of <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;<em>-weighted images. BOLD is sensitive to the concentration of deoxyhemoglobin, which acts as an endogenous <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;</em> contrast agent. The higher the concentration of deoxyhemoglobin, the shorter the <strong>T</strong>&lt;sub&gt;2&lt;/sub&gt;*</td>
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<tr>
<td><strong>b</strong>-value</td>
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<td>A parameter that determines diffusion sensitivity in DWI. The higher the <strong>b</strong>-value, the stronger the diffusion weighting</td>
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<td>Apparent diffusion constant</td>
<td>ADC</td>
<td>A quantitative measure of water diffusivity in biologic tissue. Low ADC values may reflect diffusion restriction by membranes or other microstructures</td>
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<td>Fractional anisotropy</td>
<td>FA</td>
<td>A measure of directional diffusivity within a range of 0–1. FA=0 demonstrates isotropic diffusion (in all direction), whereas FA=1 reflects diffusion along a single direction but restricted in all other directions (e.g., tubules)</td>
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Table 2. Potential applications for renal functional MRI

<table>
<thead>
<tr>
<th>Imaging Type</th>
<th>Acronym</th>
<th>Imaging Marker(s)</th>
<th>Biologic Marker</th>
<th>Potential Clinical Applications (Reference)</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic contrast-enhanced imaging&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCE</td>
<td>Perfusion</td>
<td>Hemodynamic</td>
<td>Renal artery stenosis (4)</td>
<td>Nephrotoxicity of contrast agent</td>
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<td></td>
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<td>Blood volume</td>
<td></td>
<td>CKD</td>
<td>Lack of standard imaging and analysis protocols</td>
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<td></td>
<td></td>
<td>Mean transit time</td>
<td></td>
<td>Ischemia-reperfusion</td>
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<tr>
<td>Arterial spin labeling</td>
<td>ASL</td>
<td>Perfusion</td>
<td>Hemodynamic</td>
<td>Renal tumors (6)</td>
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<td>Allograft assessment (7)</td>
<td>Complex imaging sequence</td>
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<td>Pre/diabetes (8)</td>
<td>Short $t_{1/2}$ of the labeled blood</td>
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<tr>
<td></td>
<td></td>
<td>Apparent diffusion constant</td>
<td>Morphologic and functional (flow, fluid exchange and reabsorption)</td>
<td>Renal cell carcinoma</td>
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<td></td>
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<td>Pseudo/diffusivity</td>
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<td></td>
<td>Fluid fraction</td>
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<td>Allograft assessment (7,22)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Fractional anisotropy</td>
<td></td>
<td>Diabetic nephropathy</td>
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<tr>
<td>Blood oxygen level-dependent imaging</td>
<td>BOLD</td>
<td>Relaxivity (oxygenation level)</td>
<td>Oxygenation</td>
<td>Renal artery stenosis (34)</td>
<td>Lack of standard imaging and analysis protocols</td>
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<td></td>
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<td>Response to challenge</td>
<td>Oxygen-dependent tubular transport function</td>
<td>Diabetes (30)</td>
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<tr>
<td>Magnetic resonance elastography</td>
<td>MRE</td>
<td>Stiffness</td>
<td>Tissue elasticity</td>
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<td>Sensitive to hemodynamics</td>
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<td>Fibrosis</td>
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<td>Requires hardware and analytical software</td>
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<td>Turgor</td>
<td>Renal artery stenosis</td>
<td>Time-consuming</td>
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<td>Ureteral obstruction</td>
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<tr>
<td>Spectroscopic molecular imaging</td>
<td>31P</td>
<td>ATP generation</td>
<td></td>
<td>Renal allograft (46)</td>
<td>Technically complicated</td>
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<td>Fat fraction</td>
<td></td>
<td>Fat-to-water ratio</td>
<td>Visceral lipid</td>
<td></td>
<td>Needs further validation in the kidney</td>
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<sup>a</sup>Depending on the model and the type of contrast agent, measurement of other markers (such as vascular permeability and filtration fraction) could be possible.
commonly practiced method utilizes breath-holding, particularly during the early rapid passage of the contrast agent in blood vessels (vascular phase). In the abdomen, T₁-weighted imaging is the method of choice because unlike T₂*-weighted perfusion measurement, it is insensitive to tracer extravasation and therefore affords information about vascular permeability.

Ultrasmall paramagnetic iron oxide (USPIO) particles and gadolinium-chelates have been used as contrast agents for renal hemodynamic assessments (2,3). USPIO particles, tens of nanometers in diameter, remain initially intravascular and are eliminated from the blood pool by the reticuloendothelial system. Therefore, models originally developed for brain perfusion measurement, which

Figure 1. | Dynamic contrast-enhanced magnetic resonance imaging–derived images in a swine unilateral renal artery stenosis. (A) The stenotic (right) and the contralateral (left) kidneys at baseline (a) and at the vascular (b) and tubular (c) phases. High cortical blood flow results in high contrast between the cortex and medulla during the vascular phase. (a and b) The white arrow shows the arrival of the contrast bolus in the aorta (a) and in the cortex (b) (during the contrast agent transition), whereas the red arrow shows the medulla. (c) The physiologically hypoperfused medulla shows visible enhancement mainly during the tubular phase. (d) Finally, as contrast media wash out from the tissue, their appearance in the stenotic kidney calyx is delayed compared with the contralateral kidney. (B) Typical magnetic resonance concentration-time curves, with vascular, proximal tubular, Loop of Henle, and distal tubular transitions. D, distal tubular; L, Loop of Henle; P, proximal tubular; V, vascular.
assume no contrast agent leakage from the microvasculature, can be applied for description of USPIO kinetics. Such models with a single vascular compartment are simple in nature, but do not afford information about kidney filtration. There is currently no Food and Drug Administration (FDA)-approved USPIO available and its use remains experimental.

On the contrary, gadolinium-chelate may diffuse out of the microvasculature, and a description of its kinetics demands more sophisticated models with two or more compartments (e.g., vascular, tubular, and extravascular), often describing the exchange rates between compartments (e.g., GFR or vascular permeability). Renal perfusion (ml/100 ml tissue per minute), blood volume (a fraction of total parenchymal volume), plasma mean transit time (seconds), time-to-peak (seconds), and regional filtration fraction (ml/100 ml tissue per minute) are useful functional parameters derived from multicompartmental models. Selection of a suitable mathematical model is based on the desired choice of markers and the validity of its underlying assumptions for a specific pathologic condition. Importantly, data analysis mandates selection of the region of interest in accordance with the underlying assumptions. For example, models that presume conservation of the contrast media require probing the entire kidney (in which the agent usually remains throughout the scan) and provide global information, whereas those that allow for contrast translocation during scanning permit more localized information.

The challenge for MR perfusion is the identification of significant hemodynamic and functional impairments. Speculatively, DCE may be useful in pathologic conditions that affect parenchymal perfusion through dysregulation, atherosclerosis, microvascular rarefaction, or even inflammation-associated renal function impairments. Yet DCE is reliable mostly in detecting pronounced hemodynamic alterations such as renal blood flow impairment at renal artery stenosis $\geq 80\%$ (4), above which a severe stenosis compromises flow (5). Such drastic changes may also occur in treatment of intrinsically hyperperfused tumors or during ischemia-reperfusion.

**ASL**

ASL-MRI is noninvasive and utilizes arterial blood as the contrast tracer. This method is particularly attractive as an alternative to DCE for renal applications because it eliminates the need for exogenous contrast media with possible adverse effects, particularly in patients with compromised kidney function. However, due to some limitations, ASL is primarily used for cortical perfusion measurement, and technical complexity has restricted its application primarily to research.

Using ASL, perfusion is measured by acquiring a set of labeled (tagged) and nonlabeled (control) images. Spin labeling (or tagging) involves inversion of the magnetization of arterial blood using a radiofrequency pulse. Once the labeled blood reaches the kidney and replaces the untagged blood, it reduces the intensity of the MR signal. Subtracting labeled from control images provides perfusion-weighted images with a low signal to noise ratio (SNR). Absolute perfusion can be quantified from a set of perfusion-weighted images with various delays between tagging and acquisition. The total ASL acquisition time depends on the number of perfusion-weighted images acquired, from tens of seconds to several minutes.

Thus far, ASL perfusion measurements in renal cell carcinoma (RCC) and allografts have shown promise. In patients with advanced RCC, ASL can evaluate outcomes of therapy, taking advantage of the high perfusion in tumors (6). Moreover, perfusion might indicate the stability of renal allograft function. Transplanted kidneys often have lower perfusion than native kidneys, yet a severe decline could indicate ischemic injury and functional deterioration (7). A recent study showed that ASL is also promising for assessing renal perfusion in patients with metabolic syndrome and detecting hemodynamic responses to pharmacologic interventions (8).

**GFR**

The fundamental assumption in GFR estimation using contrast-enhanced imaging is that the agent has a filtration rate similar to the body fluids. Methodologies applied to estimate GFR from DCE-MR images all rely on similar concepts to differentiate the extracted (filtered) tracer from that in the blood. Contrast media in the blood rapidly circulate through the parenchymal vasculature, but slowly accumulate and flow in the tubules when extracted. Whereas earlier studies utilized mathematically simple models, such as graph-based Patlak (9) and Upslope (10) methods, sophisticated models involving three or more compartments have evolved in recent years (11). The usefulness of noninvasive single-kidney GFR measurements prompted consideration of models with additional compartments, which afford a broader range of hemodynamic markers. A separable multicompartment model may be more reliable than the widely used Patlak method for estimation of single-kidney GFR (12), yet the correlation between standard radioisotope measures and the Patlak method was stronger compared with the compartmental approach (13). Nevertheless, there is yet no reference standard for a multicompartmental model.

A concern for GFR measurement, particularly in patients with CKD, is the potential adverse effects of gadolinium-based MR contrast agents like nephrogenic systemic fibrosis (14), which is linked to a high cumulative dose of gadolinium (15). Notably, although clinical protocols utilize 5–20 mM of gadolinium-based contrast agents, GFR measurements with a dose as low as 1.4–2.8 mM are feasible (16), yet a dose of gadolinium that is completely safe to use in patients with severely impaired renal function has not been identified.

**Diffusion-Weighted Imaging**

Diffusion-weighted imaging (DWI) MRI is a powerful method that provides several parameters that describe the restriction imposed by microstructures on Brownian random motion of water molecules in biologic tissues (Figure 2), and is thereby sensitive to morphologic changes. The method requires no exogenous contrast agent and is therefore clinically applicable; the acquisition times (<1 minute) are usually short enough to collect several slices within few breath-holds. The apparent diffusion constant (ADC), the DWI quantitative index, describes the average
diffusivity of water molecules in all three directions, and is determined by fitting the curve of DWI-MR signal intensity versus b-values, a parameter that determines the diffusion weighting, to an exponentially decaying curve. Despite its high potential, the application of DWI has been limited to research. Lack of a standard protocol, ADC dependency on b-values, and complexity of result interpretation are some of the issues restricting the renal application of this technique.

DWI has been used to evaluate a variety of renal pathologies, including lesions, acute and chronic disease, and allografts. Most pathologic conditions, including acute and chronic failure, chronic ureteral obstruction, and pyelonephritis, reduce ADC in the cortex and medulla compared with healthy kidneys (17). DWI differentiated stable from deteriorating allograft function in transplant patients, whereas ADC correlates with GFR in patients with renal artery stenosis (18). Decreases in ADC have been reported in RCC, although inflammatory lesions impose similar diffusion restrictions (19). A lower ADC might be consequent to increased cellularity that imposes barriers to free diffusion of water (19) or to accumulation of fibroblasts (20).

Figure 2. | Diffusion-weighted magnetic resonance imaging, with different maps that reflect the diverse parameters that can be derived. (A) Anatomic MR image. (B) Biexponential signal decay consistent with pseudodiffusivity (fast decaying perfusion and tubular flow dependence) and diffusivity (slowly decaying pure tissue diffusion dependence) components. (C) Apparent diffusion constant map from monoexponential decay model. (D) Pure tissue diffusivity map. (E) Pseudodiffusivity map representing tubular fluid and microvascular blood velocity. (F) Perfusion fraction (fluid fraction) map calculated using a intravoxel incoherent motion biexponential decay model. DWI, diffusion-weighted imaging.
signal by their different b-value dependency (21). For b-values, >300 s/mm² diffusion is the dominant mechanism of decay of the MR signal, whereas it is attributed to tubular flow, perfusion, and diffusion for smaller b-values. The model has decreased the variations in diffusion values reported in the kidney, but at the same time has added to the complexity of result interpretation. Intravoxel incoherent motion parameters are sensitive to tissue structure, fractional (tubular and vascular) fluid content, and their velocities. These markers have been used in early experimental studies to distinguish benign renal lesions from malignant tumors, because increased vascularity in malignant tumors is believed to increase perfusion fraction and decrease tissue diffusivity (7). Yet, given the complexity of kidney and interrelated fluid dynamics, further validation studies are necessary.

Diffusion tensor imaging (DTI) provides greater details than DWI about diffusion of free water in tissues. This information can be translated into elaborate markers such as fractional anisotropy (FA), which indicates whether water molecules are free to diffuse equally in all directions (isotropic diffusion FA = 0), or are restricted in some (anisotropic diffusion). FA = 1 corresponds to diffusion only along one orientation. Graphical maps to illustrate tissue microstructure were originally developed to detect integrity of neural tracts, and are therefore termed tractography. Several recent studies have reported higher sensitivity of FA compared with ADC to detect renal pathomorphology (22,23). Moreover, early application of DTI tractography revealed impaired medullary microstructure in dysfunctional allograft kidneys, in contrast to its highly organized microstructure in healthy kidneys (22). The utility and potential applications of this novel technique remain to be explored. Some drawbacks to DTI are time-consuming acquisitions and data processing, which may take hours.

Figure 3. | Renal BOLD MRI and physiological restricting factors. (A) Representative anatomic reference (a) and BOLD maps before (b) and after (c) administration of furosemide. Furosemide reduces oxygen-dependent tubular transport in the medulla and improves medullary oxygenation (drops on the scale toward green-blue shades). The response to furosemide is measurable by comparing the areas of the hypoxic regions and/or the change in average $R_2^*$ magnitude. (B) Parameters that may affect BOLD magnetic resonance images. Fibrotic tissues can restrict oxygen exchange between the microvasculature and tissue, so that due to low oxygen diffusivity the vascular oxygenation (sampled by BOLD) remains high despite tissue hypoxia. The three bottom squares represent relative contrast in a $T_2^*$-weighted image, which can be affected by density of capillaries or hemoglobin (e.g., hematocrit). Higher concentration of hemoglobin results in faster decay of the magnetic resonance signal and gives rise to dark regions interpreted as hypoxic tissue, without necessarily representing tissue oxygenation. BOLD, blood oxygen level–dependent.
Blood Oxygen Level–Dependent MRI

Blood oxygen level–dependent (BOLD) MRI is a unique tool that is currently clinically available for renal imaging research. The technique was initially developed for neuroimaging but found applications in different tissues and pathologic conditions due to its noninvasive nature (24). BOLD is sensitive to the blood concentration of paramagnetic deoxyhemoglobin, which acts as a MR contrast agent. Increased concentration of deoxyhemoglobin results in shorter $T_2^*$ (faster MR signal decay). The BOLD index, $R_2^*/T_2^*$, is considered a measure of tissue oxygenation level or hypoxia, based on the assumption that blood and tissue oxygenation are at tight equilibrium. Notably, some experimental investigations have challenged this assumption (25). Moreover, some pathologic conditions, like fibrosis, may restrict oxygen diffusion and prevent equilibrium (Figure 3), resulting in an oxygen gradient across the microvascular lumen, in which case blood oxygenation no longer represents tissue oxygenation. Nevertheless, BOLD remains the most popular technique to experimentally measure tissue oxygenation in vivo. The acquisition time is relatively short (1–5 minutes) and collected over several breath-holds. Its sensitivity to detect differences in oxygenation improves at higher fields, because $R_2^*$ magnitude is scaled by magnetic field strength (26).

Renal oxygenation has been used as an index of kidney allograft dysfunction and acute transplant rejection. Lower medullary $R_2^*$ values in acute renal transplant rejection (27) may represent higher oxygen bioavailability in the intrinsically hypoxic medulla secondary to impaired metabolism and halted tubular transport function (28). BOLD has also been used to study renal oxygenation in several animal models of diabetic nephropathy (29,30). Renal oxygenation likely changes in only advanced disease, because lower oxygenation is observed in the outer medulla of rats with diabetic nephropathy (29), but not in prediabetic, obese swine (31).

In a model of acute renal arterial occlusion, BOLD revealed that increases in $R_2^*$ paralleled the level of occlusion and reduction of renal blood flow (32). Indeed, patient with significant (33), but not moderate (34), renal artery stenosis show decreased renal oxygenation compared with essential hypertension. In addition to renal hypoxia, the use of pharmaceutical maneuvers permits assessment of oxygen-dependent tubular transport function (35). Furosemide, an inhibitor of the Na/K/Cl cotransporter in the thick ascending limb, has been used to evaluate medullary tubular function in a variety of renal pathologic conditions (36). Selective challenges for cortical transport activity need to be developed in order to probe cortical tubular function.

A recent study showed that the basal cortical and medullary BOLD signal was nonspecific for discriminating patients in a large cohort with diverse chronic renal diseases (37). These observations subsequently raised methodological questions (38), because BOLD uses deoxyhemoglobin as the contrast agent, and pathologic conditions (e.g., anemia or ischemia) that affect the hematocrit, microvascular density, or regional renal blood volume may nonuniformly influence the signal in a heterogenous population (39). Moreover, BOLD measurements are prone to susceptibility artifacts caused by bowel gas, which increases $R_2^*$ values and might be erroneously considered as hypoxic regions. The severity of the artifact increases at higher magnetic fields, and warrants careful selection of regions of interest. Notably, analytical methods utilizing histogram-based tools that recognize the variability of the BOLD signal intensity within the regions of interest may be capable of detecting differences (40) and introduce new markers beyond the traditional mean of $R_2^*$ value, such as their distribution (41,42).

Emerging Methods

Elastography

Magnetic resonance elastography (MRE) is a noninvasive imaging technique that utilizes translocation of mechanical shear waves to estimate tissue stiffness (Figure 4). Based on the assumption that excessive extracellular matrix deposition in fibrotic tissues increases their stiffness, MRE-derived stiffness has been used as an index of fibrosis. The feasibility of using MRE in the kidney has been demonstrated in transplant patients (43) and in swine renal artery stenosis (44,45). Interestingly, studies utilizing graded renal ischemia demonstrated that hemodynamic modulation of renal cortical stiffness hampers discrimination of fibrotic from nonfibrotic kidneys (44). However, MRE is capable of detecting fibrosis in the intrinsically hypoperfused medulla (45), which is less dependent on perfusion pressure. Understanding of underlying physiologic processes and development of appropriate models will likely increase the use of this novel technique (e.g., for monitoring evolution or regression of kidney fibrosis in abnormalities such as ureteral obstruction).

Molecular Imaging

$3^1$P MR spectroscopy was one of the earliest applications of molecular MR in kidney. Renal failure is often accompanied by a loss of ATP and progressive formation of inorganic phosphorus. Therefore, the ratio of phosphomonoesters to inorganic phosphorus is used as a marker for renal metabolism and allograft viability (46). Recent advances have

![Figure 4. Magnetic resonance elastography in swine unilateral renal artery stenosis. Lower stiffness (less red color) in the cortex of the stenotic kidney (right) compared with the contralateral kidney (left), despite greater fibrosis, is a consequence of lower perfusion pressure (and turgor) distal to the stenosis. CLK, contralateral kidney; STK, stenotic kidney.](image-url)
improved the quality of data acquisition in the kidney by utilizing chemical shift imaging; however, due to low SNR, the imaging resolution remains far lower than conventional MRI (47).

Fat Fraction

Fat fraction imaging-based methods used to quantify renal fat content (48) rely on the spectroscopic imaging method originally proposed by Dixon in 1984 (49). The technique involves acquiring in-phase (water + fat) and out-of-phase (water − fat) images to generate water-only and fat-only images (Figure 5). In the liver, quantification of hepatic fat becomes inaccurate in the presence of high fat content (50). Due to its lower fat fraction, it is unlikely that this issue limits the application of this method in the kidney. Nevertheless, fat quantification using MR is new in kidney applications and further investigations are needed to evaluate this method, which may in turn allow evaluation of the significance and clinical or pathologic correlates of renal adiposity.

Functional MRI in the kidney has come a long way and has become an indispensable research tool. All of the above-mentioned methods are noninvasive and can potentially be translated to clinical protocols. However, the lack of standardized acquisition and analysis protocols often limits functional MRI techniques. Some tools, such as DCE perfusion and GFR measurements, have already been extensively investigated in clinical trials. Nevertheless, more sophisticated and elaborate models are needed to address current limitations. BOLD and ASL are particularly promising techniques with potentially broad future clinical applications. Like all imaging techniques, they are based on assumptions, which might not always faithfully reflect the conditions in vivo and may introduce errors or impose limitations to the applicability of the techniques. DWI, DTI, and the emerging methods are powerful techniques that can provide a diverse range of biologic markers. However, additional studies are required to fully understand these markers and their association with pathologic conditions. Despite some shortcomings and limitations, functional MRI remains one of the most powerful and versatile imaging approaches available today. In particular, these functional methods provide valuable information and will remain essential for future research and potential clinical applications.

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