

Imaging Techniques in Acute Kidney Injury

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Multi-photon microscopy · Ultrasound · MRI · Acute kidney injury · Ischemia · Sepsis

Abstract

Multi-photon microscopy, along with advances in other imaging modalities, allows investigators the opportunity to study dynamic events within the functioning kidney. These emerging technologies enable investigators to follow complex heterogeneous processes in organs such as the kidney with improved spatial and temporal resolution, and sensitivity. Furthermore, the ability to obtain volumetric data (3-D) makes quantitative 4-D (time) analysis possible. Finally, use of up to three fluorophores concurrently in multi-photon microscopy allows for three different or interactive processes to be observed simultaneously. Therefore, this approach complements existing molecular, biochemical, pharmacologic and radiologic techniques by advancing data analysis and interpretation to subcellular levels for molecules without the requirement for fixation. Its use in acute kidney injury is in its infancy but offers much promise for unraveling the complex interdependent processes known to contribute to cell injury and organ failure. Also, recent advances in other imaging techniques offer potential clinical diagnostic tools to study acute kidney injury in animal models and in patients.

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Introduction

Developments in kidney imaging over the last decade have provided researchers new and tremendously in-depth insights into complex yet highly interdependent processes. A significant advance in these developments has been the emerging technology of studying cells within their natural living environment, rather than in isolated ex vivo controlled settings. This gives the unique opportunity of analyzing cellular pathophysiology and the effects of potential treatments in the context of an intact functioning organ. It also offers hope for additional diagnostic tools for diagnosis, stratification and prognostic purposes. The purpose of this review is to emphasize newer imaging techniques that have application to pre-clinical and potentially clinical studies.

Multi-Photon Microscopy

The potential to image deeper, with far less phototoxicity, into biological tissue was accomplished by utilizing multi-photon microscopy where increased penetration (up to 200 μm in the kidney) occurs from the unique photophysics of multi-photon fluorescence excitation, in which fluorescence is stimulated by the simultaneous absorption of two low-energy photons by a fluorophore [1–3]. It also allows for utilization of multiple fluorescent

probes simultaneously, enabling labeling of different physiological compartments. Distinguishing these fluorescent emissions from endogenous or auto-fluorescence is also easier and enhanced in multi-photon fluorescence microscopy, as compared to confocal microscopy, as the fluorescence excitation occurs only at the focal point of the excitation beam. Therefore, out of focus fluorescent excitation is eliminated [2].

Table 1 lists the possible types of data that can be acquired using multi-photon imaging of the kidneys. Figure 1 shows renal cortical images under physiological states (fig. 1a) and during acute kidney injury in a rat model of sepsis (fig. 1b). Reduced glomerular filtration, proximal tubule cell injury, apoptosis, reduced PTC endocytosis, reduced RBC flow rates, and increased WBC adhesion have been visualized in models of acute renal injury. Migration of WBC out of the microvasculature has not been seen up to 24 h after injury.

Yu et al. [4] have developed a quantitative ratiometric approach using a generalized polarity (GP) concept that was implemented to analyze the multidimensional data obtained from multi-dextran infusion experiments, the concept being the comparison of relative intensities of two fluorescent dyes. Ratiometric-imaging methods are relatively independent of the amount of fluorescent probes injected, the excitation power and the depth of field being imaged. These properties are particularly advantageous for the quantitative imaging of animals where there is variability in the quantity of dyes injected, the appropriate levels of laser power used, and imaging depth. In addition, using ratiometric techniques also minimizes spatial variations of the fluorescence signals across the field of view due to detector/sample nonuniformity. Finally, these investigators were able to quantify GFR based upon the disappearance (filtration) of a small molecular weight dextran, compared to a nonfiltered fluorescence dextran, over time.

Intracellular – Endocytosis, Trafficking, Transcytosis

Intracellular uptake, distribution and metabolism can be studied and quantified once the fluorescent probe has entered the cell. Using multi-photon microscopy it is now possible to observe and quantify endocytosis occurring across the apical membrane of the proximal tubule cells [1]. Furthermore, it is possible to follow the intracellular accumulation and subcellular distribution over time in the same animal, and to undertake repeated observations in the same animal at varying intervals over days to weeks. Such experiments are particularly useful in understanding drug delivery for acute kidney injury states.

Table 1. Investigational uses for multi-photon microscopy

Glomerular	Size/volume
	Permeability/filtration
	Fibrosis/sclerosis
Microvasculature	RBC flow rate
	Endothelial permeability
	WBC adherence/rolling
	Vascular diameter
Cellular uptake	Cell type-specific uptake
	Site – apical vs. basolateral membrane
	Mechanism – endocytosis vs. carrier/transporter mediated
Cellular trafficking	Intracellular organelle distribution
	Cytosol localization
Cellular metabolism	Fluorescence decay over time
Cell toxicity	Cell injury in necrosis, apoptosis
	Surface membrane/blebbing
	Mitochondrial function
	Glomerular filtration rate determination

Intracellular organelles such as mitochondria and lysosomes can be studied in acute injury states by specific labeling of these organelles and quantifying individual number and fluorescence potential of respective organelles. DNA fluorescent markers can help identify specific cell types based on their nuclear morphology (e.g. nuclei of podocytes are characteristically bean shaped, while endothelial cells have characteristic flattened elongated morphology). It also permits evaluation of intranuclear uptake of other fluorescent compounds in disease and therapeutic states, and analysis of necrosis and apoptosis [5].

Glomerular Permeability

Glomerular permeability and filtration of different sized compounds across glomerular capillaries can be quantified and visualized using Munich-Wistar rats with surface glomeruli (100 μm in diameter). Areas of interest can be defined and isolated and fluorescence intensities measured to obtain quantitative data. By using the change in GP or ratiometric methods, it is possible to quantify glomerular permeability by measuring relative change intensities of dyes in the bloodstream or within the Bowman's space [4]. Filtration and clearance of smaller size molecules is typically faster than larger-size molecules. By using two different-sized fluorescent dextrans, it is thus possible to measure glomerular filtration fraction by

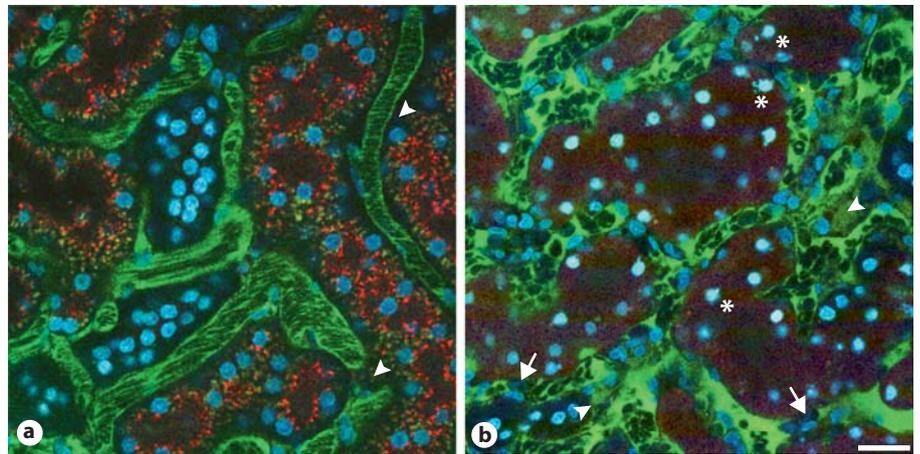


Fig. 1. Intravital kidney imaging showing endothelial and epithelial cells dysfunction during sepsis. **a** A rat under physiologic conditions was given a large 500-kDa amount of fluorescein dextran (green) to label the microvasculature, Hoechst 33342 (cyan) to label nuclei systemically, and a small 3-kDa amount of rhodamine dextran (red). Circulating red blood cells (RBCs) within the microvasculature appear as black streaks as the 500-kDa dextran (green) fills the plasma space but remains excluded from the RBCs. Proximal tubule cells with early endosomes incorporating the small 3-kDa dextran (red) are easily distinguished from distal tubules (center) that do not internalize the small dextran but incorporate higher intensity of the nuclear dye. Note the lack of flux

of the 500-kDa dextran into the interstitial space under physiologic conditions (arrowheads). **b** A rat kidney 24 h after cecal ligation and puncture to induce sepsis. Alterations in the RBC flow can be seen as nucleated white blood cells (arrows) which obstruct and hinder flow. Also noticeable is the flux of the 500-kDa dextran (green) into the interstitial space between the microvasculature and tubules (arrowheads). Proximal tubule cell accumulation of the 3-kDa dextran (red) is minimal and seen as cytosolic staining. Also distinguishable is the appearance of apoptotic nuclei (asterisk) and increased nuclear fluorescence associated with nuclear condensation. Bar = 20 μm .

measuring the changes in concentration in the bloodstream over time of each dextran.

Proximal Tubule (PT) Reabsorption

Since many acute kidney injury states affect the PTs, it is very important to be able to study the reabsorptive profile of the tubular epithelium and its recovery with or without therapeutic intervention. It is possible to evaluate the reabsorptive properties of the PT by: (1) direct observation of the epithelial cells and lumen of the PT, (2) luminal GP changes in the PT, and (3) comparing the change in GP values from within PT lumen with those from within the Bowman's capsule [1–4].

Red Blood Cell Flow Rates

Multiphoton microscopy can also be utilized to study and quantify red blood cell (RBC) flow rates in the microvasculature. It is possible to image and differentiate the motion of RBCs in the renal cortex microvasculature. RBCs exclude the nonfilterable fluorescent dye used to label the circulating plasma and consequently appear as dark, nonfluorescent objects on the images. The acquisition of repetitive scans along the central axis of a capil-

lary (line-scan method) gives the flow of RBCs, which leaves dark striped bands in the images, where the slope of the bands is inversely proportional to the velocity; the more shallow the slope, the faster the flow rate [6]. Using standardized vessel length, diameter and angles, it is possible to calculate the RBC flow rates in different states, e.g. ischemia, sepsis, and response to specific treatments [7–11].

Inflammation and Leukocytes

Inflammation is being increasingly recognized as an important and central process in the initiation, maintenance and progression of acute and chronic kidney injury. Hence, understanding the dynamic roles and functions of different leukocytes and their interactions with soluble and endothelial cell factors is key to develop and test preventive and therapeutic strategies. Multi-photon microscopy provides the opportunity to observe these crucial processes in vivo. The most effective method to image leukocytes in the kidney involves direct fluorescent labeling of specific WBC lineages. Fluorescent agents such as rhodamine 6G, acridine red or orange are preferentially concentrated in WBC and allow intravascular

detection. The DNA dye Hoechst, used to label all nuclei, also permits detection of WBC and differentiation of RBCs in the vascular space. Various markers are available for B lymphocytes, CD8+ T lymphoblasts, macrophages, naïve T cells, etc. [9].

Vascular Pathology

Acute kidney injury resulting from ischemia is associated with microvascular permeability defects and this is eventually linked with microvascular drop-out [11]. Various other pathological conditions affect the vascular space especially the glomerular vasculature. Apart from studying flow rates as mentioned above, using mixtures of different-sized fluorescent labeled dextrans, we can now examine the effect of injury on the microvasculature by observing and measuring the extravasation of these dextrans into the interstitium as elegantly demonstrated by Sutton et al. [12]. Furthermore, using multiple fluorescent labeling there is also the opportunity to study the effect of injury on the intricate and dynamic interaction of the endothelium with the matrix proteins such as metalloproteinases [13]. It also allows for correlation and further quantification of the relationship between the endothelial permeability and alterations in blood flow rates.

The regulation of glomerular hemodynamics is dependent on the interplay between the microvasculature, tubule and the juxtaglomerular apparatus (JGA). Peti-Peterdi and colleagues [14] have now extended their studies into actually being able to quantify renin content of the JGA in vivo in anesthetized Munich-Wistar rats using quinacrine tagging of the renin-secreting granules. They have also been able to measure the diameters of the afferent and efferent arterioles as well as glomerular volume.

Fluorescence microscopy application also extends its application to gene transfer into specific targets, e.g. tubular or endothelial cells. Green fluorescent protein (GFP) linked with the protein of interest, e.g. actin, that is cloned into an adenovirus vector, can be delivered into the urinary Bowman's space, proximal tubule lumen or superficial efferent arteriole by micropuncture techniques. The expression of these fluorescent labeled proteins is an invaluable tool in studying dynamic changes in the cell in various disease models [15].

Video Microscopy

Recent refinement of intravital videomicroscopy, combined with sophisticated image analysis, has permitted researchers to monitor microcirculation in vivo with

minimal invasion. Yamamoto et al. [16] initially utilized a small pencil-lens video microscope in ischemic rat kidneys to study changes in peritubular capillaries by directly opposing the capsule with a 1-mm tipped video microscope. The peri-glomerular microvasculature can be evaluated as well with a small incision in the capsule permitting access to the deeper tissues. The line-shift method calculation of RBC flow in these capillaries can determine the renal microvascular blood flow in ischemic as well as reperfusion states. These studies were recently extended to the human scenario by using high magnification videoendoscopy in a similar manner in human renal transplantation. This method demonstrated diminished peritubular flow occurring after reperfusion and this correlated with reductions in creatinine clearance [17].

Infra-Red Imaging

Other novel imaging techniques utilized in ischemia-reperfusion include infra-red (IR) imaging. Kirk and colleagues [18] used an advanced digital IR camera to image local temperature gradients simultaneously across the entire transplanted kidney by passively detecting IR emission. Infrared re-warming time was correlated with the subsequent return of renal function as well as a negative correlation with the regression slope of creatinine and the regression slope of BUN. The advantages of this method include providing a global whole kidney image of reperfusion instead of measurements of a single region, as well as giving information about regional defects. It can also provide valuable real-time intra-operative data and imaging which can assist surgeons in complicated surgeries and making instant therapeutic manipulations.

MRI Studies in AKI

Dendrimers can be polymerized to form nanoparticles of precise size that can be readily chelated to imaging agents such as gadolinium. Particle size is extremely important as the body handles specific size nanoparticles very differently. For instance, 2-nm particles are handled very similarly to low-molecular-weight contrast agents, but the kidney demonstrates significantly decreased renal excretion when it is 6-nm particles, and virtually no renal excretion for 11-nm particles [19]. In a rat model of tubular nephrotoxicity caused by cis-platinum, Kobaya-

shi et al. [20] observed loss of the normal outer stripe in the medulla. The loss of the normal renal architecture after the G-4 dendrimer was proportional to the degree of renal damage. Thus, dendrimer-based MR could be used to monitor specific outer medullary damage caused by nephrotoxic events such as drugs, ischemia, infection, and obstruction. Star et al. [21] have shown, in a mouse model, that dendrimer-enhanced MRI can distinguish sepsis-induced ARF from prerenal azotemia and renal failure due to ischemia-reperfusion or cisplatin. Furthermore, the injury could be detected as early as 6 h before serum creatinine was elevated, track the response to therapy, and provide prognostic information. However, the recent link of gadolinium-based contrast agents with nephrogenic systemic fibrosis may limit its use in human clinical studies of AKI.

USPIO

Magnetic resonance angiography utilizes ultra-small particles of iron oxide (USPIO) that have been developed as macromolecular agents based on iron. USPIO are 20- to 30-nm dextrans coated in a formulation chemically known as ferumoxtran-10 and are not filterable across the glomerulus. These agents circulate intravascularly and might be used to evaluate renal blood volume, flow and dynamic intravascular blood flow measurements. By 24 h, macrophages and monocytes phagocytose almost all circulating USPIO and then travel to the lymph nodes and areas of inflammation [19]. In acute ischemia-reperfusion injury, USPIO-laden macrophages accumulate in the outer medulla, corresponding to an inflammatory infiltrate induced by the ischemia [22], whereas others have demonstrated that, in renal transplant models of allograft rejection, uptake of USPIO corresponds with the loss of signal in the renal parenchyma and the degree of lymphocytic infiltration. Thus, USPIO could serve as a marker to detect early acute kidney injury.

BOLD-MRI

Blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) is a noninvasive method to assess tissue oxygen bioavailability, using deoxyhemoglobin as an endogenous contrast agent [23]. Oxyhemoglobin is a diamagnetic molecule that creates no magnetic moment as oxygen molecules are bound to iron, while deoxyhemoglobin is a paramagnetic molecule that generates magnetic moments by its unpaired iron electrons. Higher levels of deoxyhemoglobin result in increased magnetic spin dephasing of blood water protons and decreased signal intensity on T_2^* -weighted MR imaging sequences. In-

creased $R2^*$ or decreased intensity on T_2 -weighted images imply increased deoxyhemoglobin (decreased oxyhemoglobin) and decreased partial pressures of oxygen (PaO_2) in tissues. Therefore, the technique can be used to determine intrarenal oxygen bioavailability and has been used to investigate human and experimental models of kidney disease including radiocontrast nephropathy, acute allograft dysfunction, acute ischemic kidney injury, and unilateral ureteral obstruction [24]. This form of noninvasive imaging is desirable as it uses an endogenous marker and thus is free from exogenous agents and their potentially harmful side effects.

Other MR techniques recently being studied to image ATN and differentiate it from other causes of renal failure involve ^{23}Na MRI. The maintenance of the corticomedullary sodium gradient, an indicator of normal kidney function, is presumably lost early in the course of ATN. In rat kidneys at 6 h after the induction of ATN, the sodium images revealed that the sham-controlled kidney exhibited a linear increase in sodium concentration along the corticomedullary axis as compared to the ATN kidney where the cortico-outer medullary sodium gradient was reduced by 21% and the inner medulla to cortex sodium ratio was decreased by 40%. This was inversely correlated with small but significant rise in plasma creatinine and very limited outer medullary histologic ATN. Thus, it is possible that ^{23}Na MRI may non-invasively detect corticomedullary sodium gradient abnormalities to identify evolving ATN when morphologic tubular injury is still focal and limited [25].

Electron Paramagnetic Resonance Imaging

Oxidative stress plays a role in acute kidney injury and as this role is further defined, the importance of investigating the kinetics of reactive oxygen species (ROS) or related substances in vivo will be needed. One method to detect and study oxidative stress is electron paramagnetic resonance (EPR) imaging which is a technique to detect unpaired electrons. In the ischemia-reperfusion model, EPR imaging by Hirayama and Nagase [26] has shown significantly impaired renal radical-reducing activity in the early post-reperfusion state and only partial recovery of this radical-reducing activity even after serum markers have normalized. Other models of acute kidney injury such as LPS and puromycin nephrosis have also been investigated using EPR imaging.

Positron Emission Tomography

Positron emission tomography (PET) allows generation of images with higher resolution and absolute quan-

tification of biological processes such as transport activities and enzyme activities and its correlation with renal blood flow and glomerular filtration rate. Its value is further enhanced when its functional information is combined with computerized tomographic data. Using new PET tracers, it is possible that qualitative and quantitative assessments of in vivo hypoxia, apoptosis, endothelial dysfunction, signal transduction and organic cation transport can be performed [27].

Contrast-Enhanced Ultrasonography

Sonographic imaging of the kidneys is a routine procedure in clinical practice; however, conventional 2-D sonography has limitations due to the limited sensitivity of color Doppler ultrasonography (CDUS) for the detection of intracortical capillaries and deep pedicular vessels, and also the poor contrast of B-mode imaging for parenchymal disease [28]. Microbubble ultrasound contrast agents overcome these limitations allowing much improved assessment of the complete vascular supply of native or transplanted kidneys. After intravenous administration, microbubbles simply travel in through the renal microvasculature, but do not pass through the Bowman's capsule. Hence, they remain in the renal blood pool without sticking to the capillary walls, are not phagocytosed, do not reach the interstitial compartment, and are not excreted into the collecting system. Thus, their pharmacokinetics is strongly different from iodinated contrast agents and gadolinium chelates. It does have the advantage of repeated administration of microbubble contrast agents in patients with renal injury and there no toxicity has yet been reported [28].

Contrast-enhanced sonography (CES) has a much higher sensitivity and specificity and might be considered the modality of choice for the detection of infarction and cortical necrosis, particularly in ischemic renal transplants. CES provides quantitative information on microvascular perfusion of the renal allografts and offers improved diagnostic significance compared with CDUS for the detection of chronic allograft nephropathy. In contrast to conventional CDUS resistance and pulsatility indices, renal blood flow estimated by CES was highly significant related to serum creatinine in kidney allografts. Perirenal hematoma, ATN and vascular rejection are associated with characteristic changes of the time intensity curve of CES. Quantitative determination of arterial arrival of an US contrast medium in the early phase after kidney transplantation has been studied and this may identify acute rejection earlier than conventional techniques [29]. Further research, which is ongoing, into the role of CES in other disease states will be needed to establish its place in the diagnosis of acute kidney injury.

Conclusion

In summary, recent advances in imaging techniques, especially in intravital multi-photon microscopy, has now enabled investigators to employ and develop unique, tailor-made techniques to visualize the functioning kidney and analyze, in a dynamic fashion, the cellular and subcellular processes that occur in various acute kidney injury states and the response to therapy. Application of some of these techniques to patients is close at hand and will add to the diagnostic repertoire of the clinician.

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