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Advances in Imaging the Kidney and Cellular Processes

Stefan Herget-Rosenthal[a] Bruce A. Molitoris[b, c]

[a]Department of Nephrology, University Hospital Essen, University Duisburg-Essen, Essen, Germany;
[b]Division of Nephrology, Department of Medicine and the Indiana Center for Biological Microscopy, Indiana University School of Medicine, and [c]The Roudebush VA Medical Center, Indianapolis, Ind., USA

Introduction

Advances in imaging technologies have equipped researchers with extremely powerful tools to uniquely address clinically and biologically important questions that can only be accomplished in whole organ studies. In parallel with this, advances in molecular probes, transgenic approaches and new delivery techniques have allowed for the development of intravital studies that can follow and quantify events with enhanced resolution. Furthermore, rapid developments in computer sciences, specifically with applications to imaging, have removed many of the obstacles previously limiting the ability to utilize imaging techniques to study and quantify disease processes. In particular, developments in hardware, software, bandwidth, and data storage now provide the life scientist and clinician with systems that possess the necessary speed to effectively attack data-intensive processes utilizing digital imaging analysis. These imaging technologies enable the dynamic measurement of 3-, and in some cases 4-dimensional (3-D plus time) structure in organs and tissues, the measurement of chemical and biochemical composition of tissues, the expression of fluorescently labeled functional proteins, and quantification of the rates of physiological processes. Therefore, it is now possible to utilize these minimally invasive technologies across a spectrum of organs to facilitate the translation of new knowledge into the intact animal for discovery, diagnostic and therapeutic purposes. Figure 1 interrelates the different imaging modalities by showing their respective detection sensitivity and spatial resolution.

Researchers equipped with these unique and ever improving tools can utilize optical microscopy and digital image analysis to study subcellular events within cells, cell-cell interactions and integrative organ physiology, biochemistry, molecular and cellular biology. This will greatly enhance the understanding of physiologic and disease processes, developmental biology, and will hasten and improve the reliability and interpretation of preclinical data. Three major areas of development have now been combined to provide investigators studying the kidney with unique approaches to understanding biological processes in a renal specific fashion at cellular and subcellular levels. First, multiphoton microscopy offers the investigator a minimally invasive high-resolution technique with increased depth of penetration and markedly reduced phototoxicity for visualization of cell-cell and intracellular events intravitally. The reduction in phototoxicity results as fluorescence excitation occurs only at the focal point thereby eliminating out of focus fluorescent excitation within the tissue as would occur with confocal microscopy. Second, improved detectors with increased sensitivity, enhanced software and faster hardware, and new computational algorithms for 3-D analysis and quantification have allowed for more rapid, sensitive and accurate data gathering, visualization and interpretation. Finally, the revolution in fluorophores capable of reporting on a growing number of cellular processes has markedly improved the capabilities available to the investigator. Fluorescent labeling of proteins, either by genetic or chemical means of attachment using a wide spectrum of colors, allows for simultaneous multi-

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Bruce A. Molitoris
Division of Nephrology/Department of Medicine
950 W. Walnut St., R2-202, Indianapolis, IN 46202 (USA)
Tel. +1 317 274 5287, Fax +1 317 274 8575
E-Mail bmolitor@iupui.edu

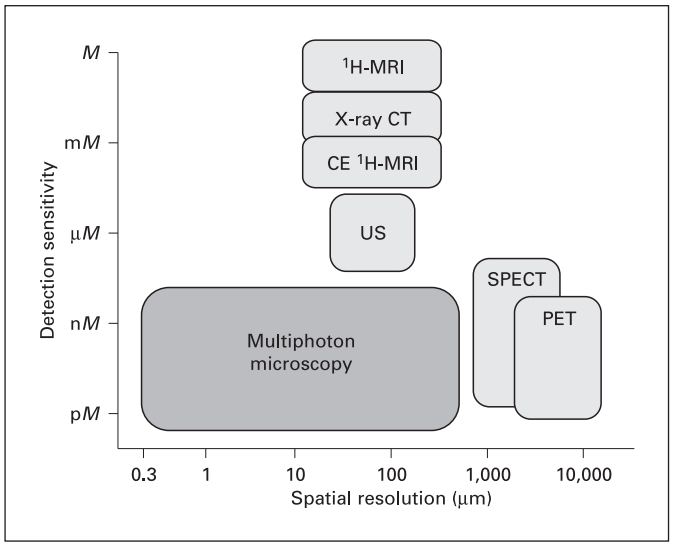

Fig. 1. Spatial resolution and detection sensitivity of intravital imaging modalities. ^{1}H-MRI = Proton magnetic resonance imaging; X-ray CT = computed tomography; Ce ^{1}H-MRI = contrast-enhanced proton MRI; US = ultrasound; SPECT = single-photon emission computed tomography; PET = position emission tomography. (We thank Dr. Gary D. Hutchins for his assistance with this figure.)

colored imaging of different cellular processes. The utility of such powerful combinations is seemingly endless, but not without challenges. Therefore, we have assembled a group of invited manuscripts to delineate the principals, characterization and potential applications, as well as imaging software programs and quantitative approaches to data analysis.

From a clinical diagnostic point of view, renal imaging modalities should ideally provide detailed information of both renal structure and function. However, in the past, the goal of imaging in clinical nephrology was limited to either providing structural or functional information regarding renal disorders. Somewhat simplifying, cross-sectional imaging by ultrasound (US), computer tomography (CT) or magnetic resonance imaging (MRI) proved useful to determine renal size, shape and position and to visualize the renal parenchyma and urinary tract. Furthermore, CT and MRI permitted an excellent evaluation of other abdominal and retroperitoneal organs for potential associated pathology that may be critical to evaluation of extrarenal pathology affecting the kidneys. Thus, potentially modifiable causes of renal dysfunction, such as urinary tract obstruction, could be readily identified. Parenchymal involvement in rarer forms of renal disease, as in cystic kidney diseases, acute interstitial nephritis or acute tubular necrosis, was considered to be associated with specific alterations in renal imaging. However, further studies demonstrated that these intrarenal findings were predominately nonspecific and an exact diagnosis could only be pinpointed in a minority of cases by cross-sectional imaging techniques. Additionally, functional alterations could rarely be assessed from the extent of morphological alterations. Radionucleotide studies provided reliable information on partial functions such as glomerular filtration rate and effective renal plasma flow. However, anatomical information derived from radionucleotide studies was limited due to their low resolution.

Substantial improvement in diagnostic renal imaging has included higher resolution, 3-D reconstruction and shorter acquisition times of cross-sectional imaging techniques. More importantly, there has been a strong tendency of cross-sectional imaging techniques towards functional imaging as clearly shown in the following reviews. As one of the first techniques, duplex sonography was applied to successfully evaluate the functional significance of vascular changes. Additionally, extra- and intrarenal perfusion can also now be studied by CT and MRI. New MRI contrast agents, with specific renal elimination characteristics, permit the estimation of glomerular filtration rate and effective renal plasma flow. In the near future, new contrast agents may even provide information on the etiology and therapeutic response of acute kidney injury, and MRI techniques may assess the state of intrarenal oxygenation. Although not yet considered first-line procedures for evaluating patients with renal disease, it is conceivable that newer cross-sectional imaging techniques may rapidly become established in clinical practice. For example, in the future, MRI could provide rapid, accurate and non-invasive information on the structure of kidneys, urinary tract and abdominal organs, intra- and extrarenal perfusion, oxygenation, glomerular filtration rate and potentially the etiology of renal diseases in a single diagnostic procedure. Besides cross-sectional imaging, advances of radionucleotide studies in renal disease will also be discussed, which now provide enhanced imaging of renal structure. Noteworthy, the current issue of *Nephron* also presents newer experimental imaging methods that have been derived from clinical techniques. Although some may never be applied in clinical medicine, they offer excellent tools to dissect pathophysiological pathways and to expand our insight into clinical renal disorders. We have tried to update the reader about the new advances enabling more accurate diagnosis and the new experimental approaches that may become tomorrow's clinical standards.