Application Brief: Nephrology

Introduction

1 in 9 adults in North America suffer from chronic kidney diseases.[1] Furthermore, acute renal failure is not an uncommon adverse event associated with many drugs. It is no wonder that nephrology research is currently one of the key focal points in biomedical research. One of the difficulties associated with kidney disease, especially chronic forms, is that *in vivo* studies must be used to track disease progression longitudinally. Furthermore, techniques that can visualize renal blood flow will greatly complement research in this area.

However, nephrology research in animal models has long been hindered by the lack of a fast, portable, high-resolution, research and animal focused imaging system that can visualize 2D and 3D kidney images, blood flow and tissue perfusion *in vivo*, in real-time, and most importantly, non-invasively. In order to ameliorate this problem, VisualSonics has introduced a revolutionary micro-ultrasound and photoacoustic imaging system that allows researchers to collect a plethora of important data over the lifespan of animals, thereby significantly reducing the number of animals needed.

Numerous satisfied nephrology researchers using Vevo® micro-ultrasound systems, from institutions such as Johns Hopkins University, Princess Margaret Hospital and NIH are publishing articles in leading journals such as *The American Journal of Pathology, Journal of the American Society of Nephrology* and *American Journal of Physiology – Renal Physiology*. This is a testament of the power and versatility of high-resolution micro-ultrasound.

Figure 1 *- Mouse kidney 3D Vasculature*

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Micro-Ultrasound in Nephrology Research

The use of micro-ultrasound in nephrology research has been regarded by leading researchers as an attractive technique for non-invasive, *in vivo* imaging of kidney micro-structures,[2] monitoring drug safety in kidneys[3] and kidney blood flow and perfusion.[4,5,6] Most research in this area is done using mice, because of their wide availability, variety of strains and ease of handling. Micro-ultrasound is especially suitable to study mice as they are the perfect size to take advantage of the maximum resolution Vevo systems offer.

For example, Sullivan *et al.* recently reported their findings in the *American Journal of Physiology – Renal Physiology* of using the Vevo high-resolution system with enhanced contrast agents to measure renal blood flow.[4] The authors were limited by the fact that conventional methods such as laser Doppler flowmetry are highly invasive and location-restricted and thus explored the use of micro-ultrasound as an exciting alternative.[4] The authors found that renal cortical and medullary rates of perfusion in response to endothelin-1 infusion were readily measured by micro-ultrasound and the results could be verified by laser Doppler flowmetry. They concluded that the Vevo system offers a rapid, non-invasive way of obtaining hemodynamic measurements with little risk to experimental subjects.[4]

Dieterle *et al.* recently published in *Current Opinion in Drug Discovery & Development* their review of different methods to monitor drug-induced nephrotoxicity in preclinical research.[3] The researchers found that the Vevo 770 system is capable of high-resolution, non-invasive imaging of not only renal artery blood flow, but even microvascular blood flow that is paramount in studies of changes such as renal artery stenosis and renal remodeling.[3] They concluded that micro-ultrasound is non-invasive, does not require radiation, does not suffer from motion artifacts and thus allows the performance of longitudinal studies of disease progression and regression.[3]

Another very interesting paper was published in *Ultrasound in Medicine & Biology* by Wang *et al.*[2] The authors examined the use of micro-ultrasound to image conscious rats.[2] Conscious imaging not only speeds up the screening process, but also decreases confounding variables such as anesthesia interactions in new drug discovery research. In this example, the authors used the Vevo system to identify unilateral congenital hydronephrosis of the right kidney in rats, which was later confirmed via histology.[2] They further visualized kidney capsule, cortex, corticomedullary junction, medulla, papilla, pelvis and hilum vasculature via micro-ultrasound in 24 kidneys.[2] It was concluded that the Vevo system allowed imaging of organ and tissue in the living state where normal tissue dynamics and physiological processes are intact and that conscious imaging of animals was possible without causing stress.[2]

Many other researchers in recent years have also been using Vevo systems as an easily accessible, applicable, fast and superior way to image kidney structure and blood flow. For a complete list of publications, please refer to **Top Nephrology Research Papers using the Vevo Systems.**

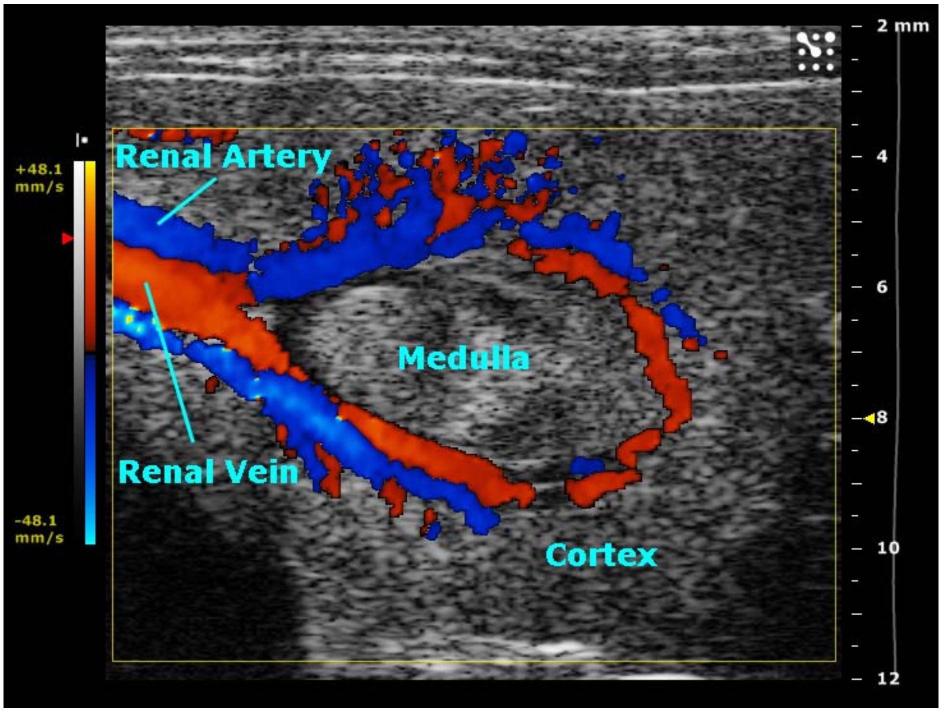

Figure 2 *– Rat Kidney Blood Flow*

Photoacoustics in Nephrology Research

Photoacoustic imaging has recently been recognized in the field of nephrology research as a hybrid technology capable of retaining the sensitivity and specificity of optical imaging while overcoming poor spatial resolution through the depth and scalability of ultrasonic imaging[8]. Song and Wang (2008) demonstrated the feasibility of photoacoustic imaging for imaging deep organ tissues, specifically the kidney in both a rat and rabbit. Because of the depth penetration offered by ultrasound, combined with the optical imaging abilities of photoacoustic imaging, both anatomical and functional imaging can be achieved within a tissue on the same plane. Specifically, oxygen saturation[10], blood volume[11] and hemoglobin content can be detected & quantified (Figure 3). Finally, photoacoustics further expands the molecular imaging capabilities for researchers through the use of nanoparticles and contrast agents, which can be targeted to specific intracellular receptors and biomarkers. This capability is useful for monitoring disease progression and therapeutic intervention.

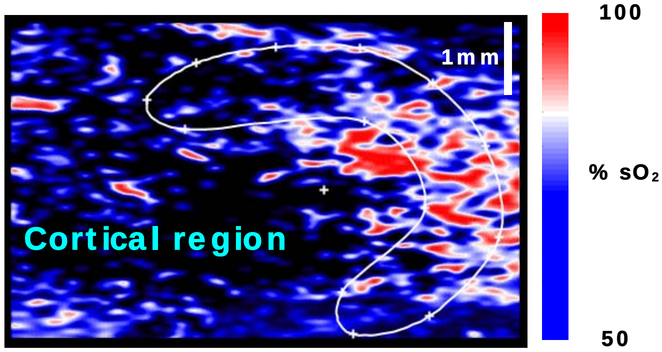

Figure 3 *–Oxygen saturation map (62% in outlined region) in mouse kidney inhaling 100% O_2 under anesthesia. Red corresponds to regions to high oxygenation levels, blue low. Outlined area is an overlay of the cortex.*

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What Can The Vevo® LAZR Photoacoustic Imaging System Do For Me?

High-frequency ultrasound and photoacoustics are unique imaging modalities for small animals non-invasive imaging in real-time. With Vevo systems, researchers now have access to a tool to conduct longitudinal studies *in vivo*. It has been demonstrated by Loveless *et al.* that micro-ultrasound produces images eclipsing MRI resolution and that the two imaging systems can be combined to validate each other's results.[7] Numerous unique tools for quantification of perfusion, as well as an open data platform allows the nephrology researcher to have full control over his/her findings.

Below is a summary of the unique value proposition VisualSonics delivers to researchers with the Vevo micro ultrasound systems:

1. **Non-invasive, *in vivo*, real-time** imaging for processes that happen over a period of time, such as chronic kidney disease, cyst development and tumor progression.
2. **High-spatial resolution up to 30 µm** allows for excellent delineation of renal and renal-related structures such as medulla, cortex, renal vein and artery, ureter, urethra and bladder in 2D and 3D.
3. **Quantification of renal function and flow**, such as pulsatility and resistivity indices, including flow in small vessels of diameter >50 µm.
4. **Unique microbubble contrast agents** allow quantification of kinetics in the microcirculation.
5. **Targeted contrast agents** for quantification of biomarkers involved in inflammation and angiogenesis.
6. **Image-guided injection** of cancer cells, stem cells, therapeutic compounds, etc. into the kidney and/or surrounding tissue without surgery.
7. **Gene transfection and enhanced drug delivery** into renal cells using the Vevo SoniGene™ system through sonoporation.
8. **Dedicated animal platform** to monitor ECG, heart rate, body temperature and respiration rates.
9. **Data export** capabilities in excel. Image/movie export capabilities in TIFF, BMP, AVI, etc.
10. **Measurement of oxygen saturation** for studies in ischemia.
11. **Nanoparticle detection and quantification *in vivo*** for targeted cellular and molecular studies.

The Vevo LAZR Photoacoustic Imaging System

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