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High-Framerate Dynamic Contrast-Enhanced Ultrasound Imaging of Rat Kidney Perfusion

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***Abstract*—Diabetic kidney disease (DKD) causes pathophysiological changes resulting in vascular injury. Conventional tests for urinary albumin and glomerular filtration rate lag behind kidney damage. We hypothesize dynamic contrast-enhanced ultrasound (DCEUS) imaging as well as power Doppler using microbubble contrast agents may serve as an early marker for DKD screening. We implement plane contrast-enhanced ultrasound on the Verasonics Vantage to perform high-framerate DCEUS and power Doppler imaging. Here, we demonstrate that high-framerate imaging does not provide significant improvements to DCEUS, making clinical machines reasonable for use in studying kidney cortex. Furthermore, we show how temporal filter-based power Doppler with contrast agents allows for the visualization and quantification of flow in the slow medullary regions of the kidney.**

Keywords—diabetic kidney disease, microbubble contrast agent, power Doppler, perfusion

I. Introduction

DKD is a deterioration of kidney function due to long-term hyperglycemia causing injury to the vasculature. Conventionally, elevated urinary albumin and decreased glomerular filtration rate are used as screening measures for DKD. However, glomerular damage occurs earlier than the presentation of conventional biomarkers [1,2]. We propose that DCEUS imaging will allow for the detection of kidney vascular damage indicative of early-stage DKD, providing an earlier marker for screening. In DCEUS, the kinetics of microbubble contrast agents flowing into a region are used to determine tissue perfusion rates.

DCEUS imaging measures blood flow dynamics by following the changes in ultrasound signal over time as a contrast agent circulates throughout the organ. A specific method of DCEUS known as "destruction-reperfusion" utilizes a high-pressure transmit to destroy microbubbles within the imaging region, and subsequent imaging measures the contrast agent's inflow from surrounding spaces. A time-intensity curve can be calculated for the region of interest and a model fit is typically used to determine rate of perfusion [3].

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A potential issue in DCEUS for kidney imaging is that clinical ultrasound scanners have limited framerates (<30 Hz), which may lead to under-sampling of faster flowing regions in the kidney such as the cortex. Therefore, we investigate the effect of increased framerate for DCEUS for improved perfusion metrics. Furthermore, high-framerate ultrasound allows for power Doppler imaging to be performed where the specific temporal incoherence of microbubbles allows for separation of contrast signal from tissue.

II. Methods

A. Animal Imaging Protocol

Adult Fisher rats (Charles River, Raleigh, NC, USA) ranging in size from 150 to 250 g, were chosen as imaging subjects. Anesthesia was started with 5% isoflurane in 1 atm oxygen and maintained at 2.5%. A 24-gauge catheter was inserted into the tail vein for contrast administration using a computer-controlled syringe pump (Harvard Apparatus, Holliston, MA, USA). The rats were secured on a temperature-controlled heating pad with the left abdomen facing upwards. Fur was removed via shaving and depilatory cream in the area of interest and ultrasound transmission gel was placed on their exposed abdomen. A water bath was placed on top of the gel and the transducer was placed in the water bath for ease of transducer translation. Upon location of the kidney, the probe was scanned across the entire region to ensure no acoustic shadowing was present. Contrast agents were manufactured in house using a lipid-shell filled with decafluorobutane gas as described previously [4]. The injection concentration was approximately 3×10^9 bubbles/mL after sterile saline dilution. Animal use protocols were approved by the University Of North Carolina School of Medicine.

B. High-Framerate plane-wave pulse-inversion imaging with angular compounding (PWPI)

Plane-wave pulse inversion (PWPI) imaging was implemented on the Vantage (Verasonics, Kirkland, WA, USA) programmable ultrasound scanner for the L11-5 transducer. The provided high-framerate imaging and flash angle sequences

were combined with pulse inversion. In flash angles imaging, time-delayed plane waves are transmitted at various angles over a range of 30 degrees (-15° to 15°). The received echoes are summed and a resulting image is reconstructed from the summed receive data. For pulse inversion, a positive and negative pulse are transmitted at each angle, which are summed as well.

For all parts of this study, imaging was performed using 3 angle compounding at 4.5 MHz and 220 kPa (MI = .104) peak negative pressure (PNP). Kusonose et al. (2018) demonstrated that greater number of angles improves the contrast-to-tissue ratio as well as tissue suppression [5]. However, due to motion artifacts being of particular concern, we chose 3 angles seeing that it provided reasonable quality images with minimal motion artifacts.

C. Dynamic Contrast-Enhanced Ultrasound Imaging

DCEUS was performed by initially imaging for 1 second, followed by a high-pressure destruction sequence to remove microbubbles from the imaging plane, and the subsequent reperfusion imaged for 8 seconds using the PWPI imaging scheme.

Microbubble destruction was performed using focused transmits across the entire imaging region at a PNP of 2.54 MPa (MI = 1.198) with 192 ray lines and 6 focal zones in depth using 64 elements and an inter-pulse duration of 30 μs.

D. Contrast-Enhanced Power Doppler (CEPD) Imaging

Although spatiotemporal filtering of ultrafast ultrasound imaging has been shown to provide high-quality power Doppler images [6,7], the singular value decomposition filter is limited for use in longitudinal studies due to the manual selection of filtering thresholds. Furthermore, the kidney medulla exhibits extremely slow perfusion rates, which would inhibit the ability of either temporal or spatiotemporal filters to extract slow-flow regions. As such, we used PWPI in conjunction with temporal filtering of HFR data to generate power Doppler images.

By using pulse-inversion imaging, nonlinear content produced by the uneven oscillation of microbubbles can be measured while tissue signal is suppressed [5].

A bandpass filter from 5-30 Hz as well as 30-100 Hz were applied to the ensemble of PWPI images. Summing the images together after filtering results in a power Doppler image pertaining to the specific frequency band that is expected to relate to slow and fast flow. The average intensity of the kidney region in the doppler images was weighted per the slice area and summed to obtain the volumetric Doppler blood flow.

E. Effect of Contrast Administration

To investigate the effect of contrast agent administration schedules on perfusion metrics, DCEUS was performed of the kidney at a single location with varying imaging framerates (15, 50, 100, and 200 Hz) and dosing schedules (N=6). The 3 infusion rates ranged from 2.1×10^8 to 3.9×10^8 bubbles/min via syringe pump.

F. Volumetric Imaging

DCEUS was performed using PWPI at framerates of 15 Hz and 200 Hz. Three-dimensional perfusion was obtained by mechanical translation of the transducer using a computer-controlled motion stage and motion controller interfaced with LabView (National Instruments Corporation, Austin, TX, USA). For imaging, a step size of 2mm was chosen to prevent overlap of imaging planes.

G. Vasoactive Drug Administration

To assess imaging methods for detecting changes in kidney perfusion, vasodilation was induced with dopamine (Sigma-Aldrich, St. Louis, MO, USA). Rats (N=7) were imaged before and after dopamine administration. As a baseline, a volumetric perfusion scan was performed, followed by dopamine administration, and another volumetric scan. To ensure no changes in bubble concentration, the dopamine was added to the contrast agent dilution. Three minutes passed after dopamine administration before imaging.

H. Image processing and analysis

In MATLAB (Mathworks, Inc., Natick, MA, USA) , perfusion metrics were obtained through taking the average intensity over time for a region of interest manually drawn around the kidney. For each time-intensity curve, a mono-exponential function was fit to the data, which is written as:

$$I = A(1-\exp(\beta t)) \quad (1)$$

Where I is the average intensity, A is the maximum intensity, and β is the slope of the curve.

The β coefficients for each imaging slice was weighted per slice area for volumetric imaging and summed to generate the volumetric β value.

III. Results

A. Effect of Contrast Administration

Streeter et al. demonstrated that there was an optimal range of contrast administration rates that yielded the lowest variances in perfusion metric β [8]. To determine whether this range would differ using HFR-PWPI imaging, we varied the dosing rate as well as the imaging framerate. The R^2 coefficient after fitting Eqn. 1 to the data was used to measure wellness of fit to the data.

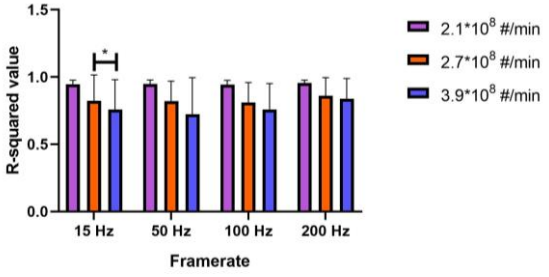

Fig. 1. Plot showing changes in R^2 coefficient in fitting the destruction-reperfusion data to the Eqn. 1. The data shows an increase in variance for higher infusion rates, however only R^2 between 2.7×10^8 and 3.9×10^8 showed statistically significant difference at 15 Hz.

As shown in Figure 1, higher contrast administration rates resulted in a slight decrease in the R^2 values for all framerates, however, significant difference (p=0.0478) was only found between the two highest infusion rates in the lowest framerate using a 2-way ANOVA test.

B. Contrast-Enhanced High-framerate Power Doppler

After destruction-reperfusion, an ensemble of 600 frames was used to generate CEPD images. These images were filtered based on low-frequency or high-frequency content, and the average of the region was used to assess perfusion. Figure 2 shows an example of low and high frequency filtering for power Doppler imaging. In the low-frequency CEPD image, contrast signal in the medullary regions is still visible which is suppressed in the high-frequency image. Low-flow regions can be enhanced using these selective filtering parameters.

C. Vasoactive Drug Administration and Volumetric Imaging

Administration of dopamine induces vasodilation as well as increased heart rate [10]. Volumetric β metrics after dopamine administration was approximately 24.9% greater pre-dopamine in the 15 Hz framerate trials, and 24.6% increase using 200 Hz framerate. The increase in β coefficients pre- and post-dopamine administration was statistically significant for both 15 Hz (p=0.0026) and 200 Hz (p=0.0108) as seen in figure 3 using a one-tailed t-test and matches expected values as seen in the literature [10].

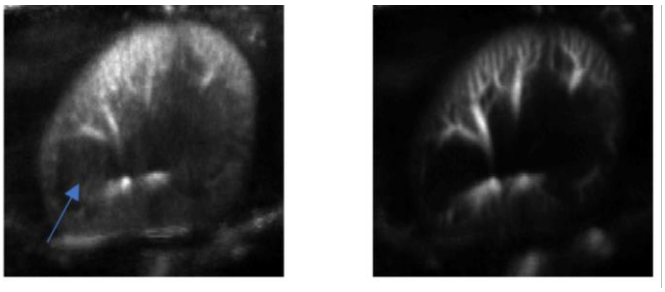

Fig. 2. Example of low-frequency (left) and high-frequency (right) CEPD images of a rat kidney. The medulla shows contrast perfusion (blue arrow) in the low-frequency image, whereas this area is removed in high-frequency filtering.

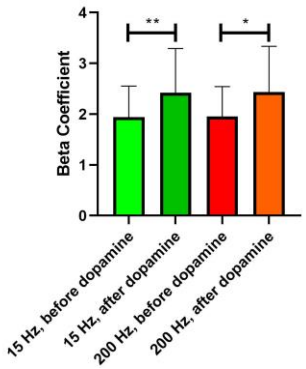

Fig. 3. Plot showing change in volumetric β coefficients pre- and post-dopamine administration.

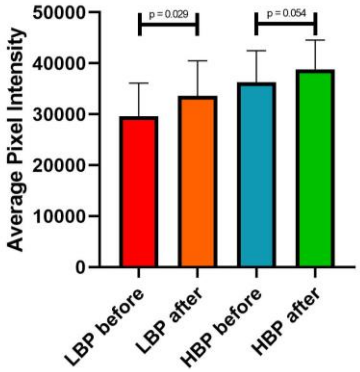

Fig. 4. Plot showing change in volumetric CEPD intensities pre- and post-dopamine administration.

Volumetric average intensity for CEPD images showed a statistically significant increase in the low-bandpass (LBP) filtered images (p = 0.029) whereas the high-bandpass (HBP) filtered data's increase was less significant (p = 0.054) as seen in figure 4.

IV. Discussion

The initial aim of this work was to determine whether high-framerate imaging benefits DCEUS in the kidney for the purposes of studying DKD. By increasing the framerate, the ability to fit the mono-exponential function to the destruction-reperfusion data does not appear to improve, while providing the same β coefficient. Furthermore, the greater limiting factor for DCEUS is the contrast administration itself, where higher infusion rates reduces the R^2 values slightly. By going to 50 Hz and greater, this effect is statistically insignificant.

A key benefit to higher framerate imaging is the ability to generate Power Doppler images using contrast agents. Although spatiotemporal clutter filtering of ultrafast ultrasound imaging has been used to generate power Doppler images in the past, the singular value decomposition (SVD) filter used is a global filter which is specific to the dataset. Thus, the manual tuning required for SVD filtering is not optimal for the longitudinal study of DKD progression. Our method of power doppler relies on nonlinear imaging to suppress tissue signal while enhancing contrast. Thus, our temporal filtering does not require higher cutoffs and allows for low-frequency (slow-flow) content to be retained, allowing for imaging of the medullary regions of the kidney.

Optimization of the power Doppler cutoffs as well as acoustic and imaging parameters are ongoing. Furthermore, comparison to conventional power Doppler and other perfusion metrics are still necessary before applying this imaging technique towards studying DKD.

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