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Enhanced Depth of Field Acoustic Angiography with a Prototype 288-element Dual-Frequency Array

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***Abstract*—Many diseases are characterized by abnormal microvasculature, which may be used as a biomarker of malignancy. Our group has developed acoustic angiography, a superharmonic contrast-enhanced ultrasound technique that uses dual-frequency transducers with low frequency transmit and high frequency receive to create high resolution, 3D microvascular maps. Prior work has focused on acoustic angiography using single-element confocal dual-frequency wobblers, but these devices have limited imaging depth and sensitivity for clinical applications. Here, we present the latest development of acoustic angiography via the implementation of a novel dual-frequency vertically stacked array. We show that this array demonstrates greater depth of field and contrast-to-noise ratio than previous wobblers and discuss future development of dual-frequency arrays for clinical acoustic angiography.**

Keywords—acoustic angiography, microbubble contrast agent, dual-frequency, microvascular

I. Introduction

Many diseases, including cancer, are characterized by abnormal microvascular morphology. Cancerous tumor growth is associated with the development of tortuous, dense, chaotic vascular networks [1]. These microvascular features may be used as biomarkers of malignancy when assessed with diagnostic imaging. However, current clinical angiography modalities, including computed tomography and magnetic resonance imaging, suffer from high costs, limited real-time capabilities, safety concerns, and poor resolutions.

Our team has developed acoustic angiography, a dual-frequency (DF) superharmonic contrast-enhanced ultrasound technique that creates high-resolution, 3D microvascular maps [2]. To do so, custom DF devices are required to transmit at low frequency (LF, 2 – 4 MHz) and receive at high frequency (HF, 20 – 30 MHz). Our prior work has focused on the preclinical development of acoustic angiography with single-element confocal annular DF wobblers, but the clinical utility of these devices is limited. Here, we present the latest preclinical and clinical development of acoustic angiography through the implementation of a novel DF vertically stacked array.

II. Methods

A. Acoustic System

The dual-frequency array (DFA) used here contains a 32-element, 2 MHz linear stack behind a 256-element, 18 MHz linear stack for confocal DF imaging with a total of 288 elements. The DFA is operated by two Vantage 256 research scanners (Verasonics, Kirkland, WA, USA) programmed for LF transmit at 2 MHz and HF receive at 15.625 MHz in a focused

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imaging scheme with 128 ray lines. To acquire 3D image stacks, a linear motion stage (Velmex, Inc., Bloomfield, NY, USA) and custom LabVIEW script (National Instruments, Austin, TX, USA) was used to translate the DFA across the image volume. Imaging was also performed with a DF wobbler transducer for comparison, which has been described in prior work [3]. For all experiments, a frame rate of 4 fps was used.

B. Microbubble Contrast Preparation

The contrast utilized in this work was a polydisperse lipid-shelled perfluorobutane-core microbubble suspension that has been previously described [4]. Lipid solution was formulated in-house and shaken in a Vialmix for microbubble formation (Lantheus Medical Imaging, North Billerica, MA, USA). The mean diameter of these microbubbles was 1.1 µm. For *in vitro* and *in vivo* experiments, microbubbles were diluted to $1x10^7$ and $1x10^{10}$ #/mL, respectively.

C. Sensitivity and Resolution

Sensitivity and resolution of the DFA were measured with a 200-µm cellulose and 100-µm PETG tube, respectively. Each tube was filled with contrast and imaged in a water tank for focal depths varying from 5 – 30 mm. Sensitivity measurements were performed at MI = 0.35 for all depths, while resolution was assessed at MI = 0.33. For each depth, 50 frames of image data were processed in MATLAB (Mathworks, Inc., Natick, MA, USA). Sensitivity was measured via contrast-to-noise ratio (CNR), defined as the mean intensity inside the tube divided by the mean intensity outside the tube in decibels. Resolution was defined as the full-width at half-maximum (FWHM) of the tube in the lateral and axial dimensions of the DFA.

D. Kidney Imaging

In vivo imaging with the DFA was performed on healthy rat kidneys (female Fischer 344 rats, Charles River Laboratories, Wilmington, MA, USA). Kidneys were chosen as an imaging target for their high degree of vascularity and interesting 3D vascular architecture. The flank above the kidney was shaved, vaporized isoflurane was used as anesthesia, and microbubbles were infused through a tail-vein catheter during imaging. Volume scans were acquired with MI = 0.48 and 0.1 mm steps between positions, and 5 frames were averaged at each position. This study was approved by the University of North Carolina Institutional Animal Care and Use Committee.

III. Results

A. Sensitivity and Resolution

Mean CNR values measured *in vitro* for the DFA and a DF wobbler are shown in Fig. 1. The DFA exhibited consistently high CNR for all focal depths between 7.5 and 27 mm, whereas the fixed focus of the DF wobbler produced CNR values that were high near the focus and fell off quickly for other depths. At the optimal depth for the wobbler (15 mm), the DFA yielded a 6.5 dB increase in CNR. The DFA exhibited optimal resolution for a focal depth of 15 mm, with mean FWHM values of 192 and 197 µm in the lateral and axial dimensions, respectively. These results illustrate the advantage of imaging with an electronic focus on a linear array over a fixed focus on a single-element probe.

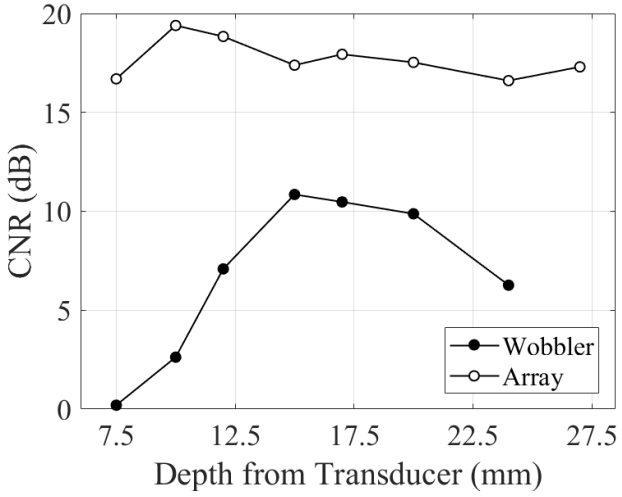

Fig. 1: Contrast-to-noise ratio (CNR) as a function of depth from the transducer surface for the dual-frequency array and wobbler probes.

B. Kidney Imaging

In vivo acoustic angiography data collected with the DFA is shown in Fig. 2. Fig. 2A provides a 3D rendering of the kidney vasculature, while Fig. 2B provides a single slice from the image stack. These images display high sensitivity to contrast signal compared to background tissue. The profiles shown in Fig. 2C correspond to the matching colored marks in Fig. 2B. The FWHMs of these vessel profiles were measured at 260, 528, and 274 µm for the green, magenta, and cyan curves, respectively, demonstrating that the DFA can detect vessels on the order of 250 µm *in vivo*.

IV. Discussion and Conclusion

The preliminary results presented here demonstrate the improvements gained by transitioning from DF dual-element wobbler probes to integrated DF arrays for acoustic angiography imaging beyond the scope of preclinical research. Previously, we have shown that DF wobblers suffer from poor imaging depth and contrast sensitivity in human breast imaging [7]. Consequently, the high sensitivity and improved depth of field observed with the DFA will be critical for the clinical translation of acoustic angiography. In addition, optimization of beamforming for this novel array design will improve image resolution. Continuation of this work will include quantitative comparison of the imaging performance of the DFA and DF wobblers *in vivo*, including image sensitivity, resolution, and depth. As this work progresses, future DFA designs will incorporate larger elevation aperture, greater number of LF elements, and appropriate lensing to further improve image quality for clinically relevant imaging targets.

Conflict of Interest

P.A.D. declares that he is an inventor on a patent describing dual-frequency imaging and is a co-founder of SonoVol, Inc., which has licensed this patent.

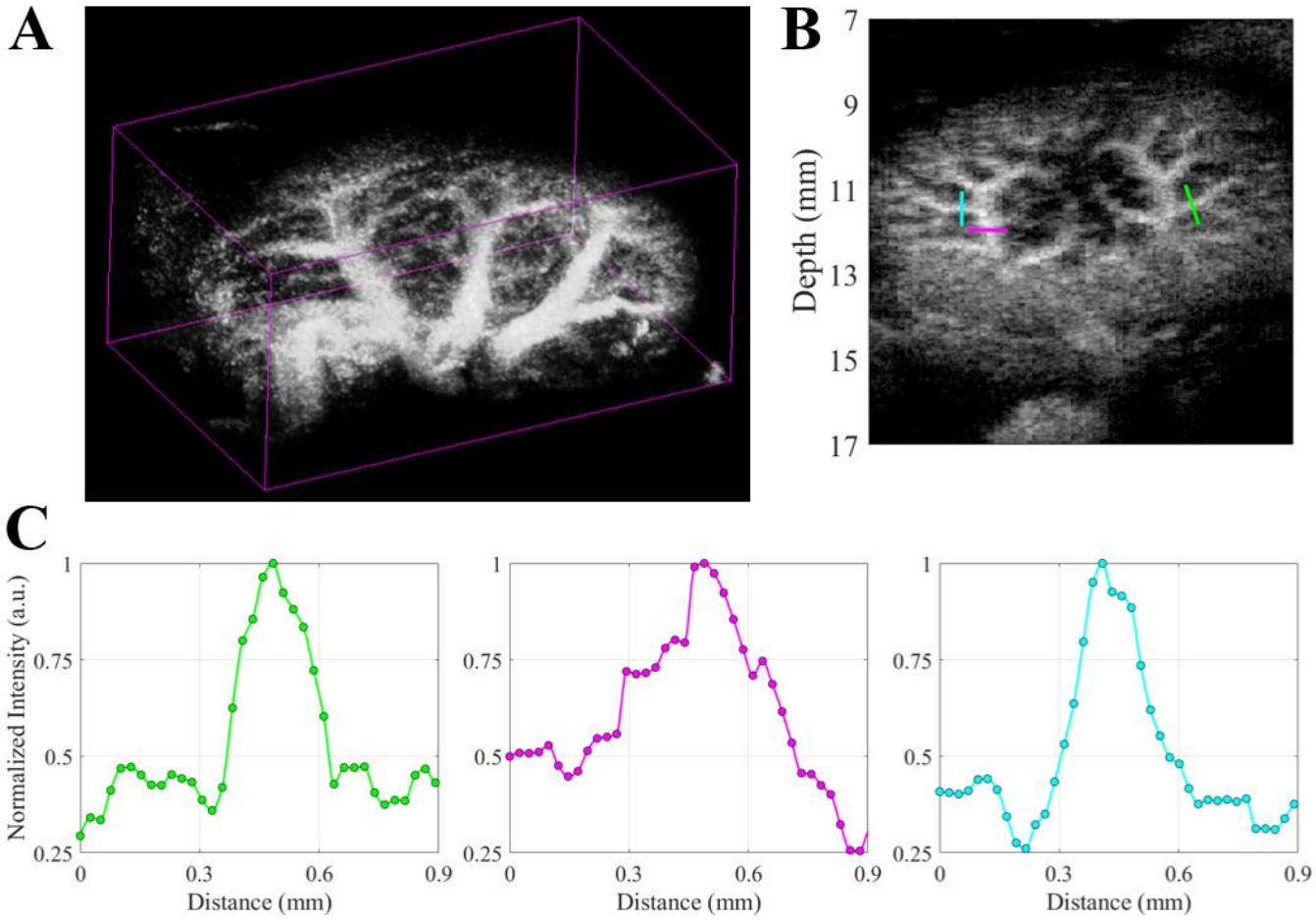

Fig. 2: In vivo acoustic angiography of rat kidney: (A) 3D rendering of renal vasculature, (B) 2D slice from 3D volume, (C) profiles corresponding to marked vessels in panel (B).

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