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In vivo imaging of ocular blood flow using high-speed ultrasound

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Abstract

Clinical ophthalmic ultrasound is currently performed with mechanically scanned, single-element probes, but these are unable to provide useful information about blood flow with Doppler techniques. Linear arrays are well-suited for the detection of blood flow, but commercial systems generally exceed FDA ophthalmic safety limits. A high-speed plane-wave ultrasound approach with an 18-MHz linear array was utilized to characterize blood flow in the orbit and choroid. Acoustic intensity was measured and the plane-wave mode was within FDA limits. Data were acquired for up to 2 sec and up to 20,000 frames/s with sets of steered plane-wave transmissions that spanned 2θ degrees where 0 degrees was normal to the array. Lateral resolution was characterized using compounding from 1 to 50 transmissions and -6-dB lateral beamwidths ranged from 320 to 180 μm , respectively. Compounded high-frame-rate data were post-processed using a singular value decomposition spatiotemporal filter and then flow was estimated at each pixel using standard Doppler processing methods. A 1-cm diameter rotating scattering phantom and a 2-mm diameter tube with a flow of blood-mimicking fluid were utilized to validate the flow-estimation algorithms. *In vivo* data were obtained from the posterior pole of the human eye which revealed regions of flow in the choroid and major orbital vessels supplying the eye.

I. Introduction

Human ophthalmic imaging was one of the earliest clinical imaging applications for high-frequency ultrasound (HFU, > 20 MHz). Ophthalmic ultrasound typically uses 10–20 MHz transducers to image the back of the eye and 30–50 MHz transducers for the front of the eye. Ophthalmic ultrasound uses much of the same technology found in the first clinical ultrasound machines from the 1970s that were based on mechanically scanned, single-element transducers operating in the low-MHz frequency range (1–5 MHz). This early clinical technology was quickly replaced with array-based systems that provided better image quality. However, low-MHz, array-based systems are not well suited to ophthalmic imaging because their resolution is not sufficient for what is needed in the eye.

One drawback of single-element systems is that they are only optimized for one imaging depth and a compromise must be found between depth of field and image resolution. Another drawback with these systems is that Doppler techniques are of minimal use to quantify blood flow in the retina, choroid, orbital vessels or anterior segment because only a limited spatial volume can be characterized at any time and, combined with motion artifacts from the patient and sonographer, it is difficult to relate a Doppler measurement to a specific region of the eye.

Unlike with single-element systems, Doppler methods can be effectively implemented with linear arrays, but traditional Doppler modes generally exceed FDA ophthalmic safety limits unless acoustic outputs are lowered to a level where little flow information is revealed. Assuming FDA limits were not exceeded, temporal and spatial resolution would still be inherently limited because image formation is line by line and, as the Doppler volume increases, more and more transmissions are required. Doppler approaches, such as color-flow, are also typically based on axial flow estimates and cannot provide information on lateral flow components. When flow is essentially through a tube, traditional Doppler modes can provide accurate estimates, but traditional Doppler is not capable of characterizing instantaneous, tortuous flow such as seen in the uveal tract (choroid, iris, ciliary body) of the eye.

Plane-wave imaging methods provide a means to overcome the limitations of traditional Doppler. Plane-wave imaging was first explored in the 1970's [1]–[3] and has been applied to *in vivo* cases including human cardiac [4] and newborn human babies [5]. The basic concept is to transmit a wide field-of-view plane wave into a medium, usually by firing all of the elements of a linear array with inter-element transmission delays that create a coherent wave front at a steered angle. The return echoes are then digitized on all of the array elements and basic delay-and-sum beamforming is implemented to generate a full 2D image from a single transmission. The rate of transmission is limited by the round trip acoustic propagation time. As imaging depth increases, maximum frame rate decreases. The major advantages of plane-wave imaging are that high-speed events can be visualized without motion artifacts and Doppler methods can be used to simultaneously obtain anatomic and flow information throughout the full 2D image. The shallow penetration depths of HFU applications make them particularly well suited to plane-wave methods. (A 37 kHz frame rate can sustain a 2-cm imaging depth.)

Here, we implement a plane-wave imaging approach to image choroidal and retrobulbar blood flow in human subjects using an 18-MHz linear array. The acoustic field of the array was characterized and phantoms were utilized to validate the data collection methods and Doppler flow estimation algorithms. Finally, human-subject data were acquired and regions of blood flow were characterized over a cardiac cycle.

II. Methods

A. Data Acquisition

Experiments were performed with a Vantage 128 (Verasonics, Redmond, WA) research platform with an 18.5 MHz probe having an 18-mm elevation focus, 0.1-mm element pitch,

0.08-mm element width and 1.5-mm element length (L22-14vLF) [6]. This relatively long focal length is better suited for imaging the back of the eye. A custom MATLAB (2014a, MathWorks, Natick, MA) script was developed to permit two modes of operation during a patient scan.

Upon initial execution, the script placed the Verasonics in a Doppler overlay mode in order to provide real-time feedback of local blood flow. This mode alternated between a set of a plane-wave transmissions transmitted with a PRF of f_a^{PRF} at a series of steered angles (total angle span of $2 * \theta$ where $\theta = 0$ was normal to the transducer) with 1.5 cycles and a fixed angle (ϕ) set of b transmissions with 4 cycles at a PRF of f_b^{PRF} . After beamforming, the steered angle set was compounded and then a B-mode image was formed. The fixed angle set was processed with standard Doppler algorithms native to the Vantage to produce a color-Doppler overlay on top of the B-mode image.

The Doppler overlay mode provided guidance for locating a region of interesting (ROI) during a human-subject scan. The PRF of the Doppler transmission and the Doppler steering angle could be changed in real time. Typically, $f_a^{\text{PRF}} > a * f_b^{\text{PRF}}$ so that once f_b^{PRF} has been selected to avoid aliasing, f_a^{PRF} will also not lead to aliasing as described below.

When a ROI was located, a high-frame-rate, long duration acquisition was initiated with a typical time of 1 to 2 s. The high-frame-rate mode transmitted sets of a steered plane waves of 1.5 cycles. The acquired data were streamed to the host computer as M blocks of N plane-wave sets and temporarily stored in RAM. The first plane-wave set, N_0 , from each block M was beamformed and displayed to provide some image feedback in order to minimize motion artifacts. The total number of transmissions in a high-frame-rate data collection was $axMxN$. After acquiring data and transferring the data to host-computer RAM, the data were briefly reviewed for any obvious motion induced artifacts and, if none, were saved to the host computer hard drive for later processing.

B. Data Processing

The acquired high-frame-rate data were post-processed with MATLAB to generate B-mode image sequences and flow information that could be overlaid on the B-mode image. The raw data were first beamformed into IQ data using custom delay-and-sum GPU beamforming tools [7], [8], each set of a plane-wave transmissions was summed together (i.e., compounded) and then saved to the host computer. This reduced the total number of image frames to MxN and the effective PRF to $f_{\text{eff}}^{\text{PRF}} = f_a^{\text{PRF}} / a$. The data were then filtered using a singular-value-decomposition (SVD) approach [9] and standard Doppler processing methods were applied to determine velocity from the Doppler spectrum using a sliding window. Doppler estimates were made for each image pixel.

C. Acoustic Field Characterization

Before human-subject experiments, acoustic pressure measurements were performed using a calibrated hydrophone to ensure that the peak acoustic pressures were within the FDA 510k limits. A calibrated hydrophone with a 40- μm acoustic element and a 60-MHz bandwidth

(Precision Acoustics Ltd., Dorset, UK) was used for the calibration. Measurements were made in the central region of the sound field with the hydrophone positioned at a range of depths. Lateral resolution was characterized using a 20- μm diameter wire with compounding of 1, 3, 5, 10 or 50 transmissions and $\theta = 10$ degrees.

D. Flow Phantoms

The algorithms used to estimate flow velocity were validated using data from two types of phantom. The first phantom was a cylindrical, tissue-mimicking gel phantom (ATS, Bridgeport, CT) attached to a DC servo motor (Fig. 1). The phantom contained scattering particles and was rotated in the plane of the linear array such that the 1-cm diameter, circular cross section was revealed in the image. The phantom provided a simple means of generating a full, continuous range of positive to negative axial velocities in a single set of data. The second phantom was a flow channel with blood mimicking fluid (BMF-US, Shelley Medical Imaging Technologies, London, Ontario, Canada) passing through at a constant volume flow rate. The flow phantom contained several channels of different diameters, but only the 2-mm diameter channel was used for the experiments. Data were collected with the linear array tilted relative to the flow with the flow passing in plane or through the plane of the linear-array sound field.

E. Human-subject Scans

The studies followed the principles of the Declaration of Helsinki. The research procedure was approved by the Institutional Review Board at Columbia University Medical Center and informed consent was obtained from the subjects. Scans were acquired with the subject in a seated position with both eyes open. Having both eyes open permitted the patient to fixate on a distant target and helped reduce unwanted eye movement during scanning. The probe was placed in contact with the lower eye lid after application of a coupling gel. Images of the optic nerve head and macula region were captured.

III. Results

A. Acoustic Field

Peak negative acoustic pressure versus distance from the linear array was measured with the hydrophone. At each axial depth, data were taken in the elevation plane with 80 μm spacing and a set of elevation scans were acquired spaced at 0.2 mm. The peak pressure at each depth was used for measurements of derated spatial-peak pulse-average intensity ($I_{\text{sppa},3}$), derated spatial-peak time-averaged intensity ($I_{\text{spta},3}$), and Mechanical Index (MI).

The measured peak acoustic parameters were $I_{\text{sppa},3} = 3.1 \text{ W/cm}^2$, $\text{MI} = 0.07$, and $I_{\text{spta},3} = 14 \text{ mW/cm}^2$ with the PRF at an extreme case of 40 kHz. These values were within the FDA 510k ophthalmic safety limits of 28 W/cm^2 for $I_{\text{sppa},3}$, 0.23 for MI, and 17 mW/cm^2 for $I_{\text{spta},3}$. Using conventional methods of linear array excitation with an $F\# = 4$ and a 47 element sub-aperture, the MI was 0.32 which exceeded the FDA limits.

Lateral resolution was determined by acquiring images of a 20- μm wire. Using compounding of 1, 3, 5, 10 or 50 transmissions and $\theta = 10$ degrees, the -6-dB beamwidths ranged from 320 to 180 μm , respectively.

B. Flow Phantoms

A flow phantom with a 2-mm diameter tube was used to characterize continuous, constant flow in one direction. The peak velocity of the flow was 51.3 mm/s and the probe was tilted at 20 degrees relative to the flow channel. High-frame rate data were acquired with $a = 10$ angles and $\theta = 5$ degrees. The data were acquired at a frame rate of 20 kHz which, after beamforming and compounding, resulted in an effective frame rate of 2 kHz. The data were processed to obtain peak Doppler velocity at each pixel location and then corrected for the relative Doppler angle between the axis of the probe and the flow tube. Plots of the flow in the lateral (Fig. 2a) and elevation (Fig. 2b) directions reveal peak values in the central region of the flow in line with the expected peak value.

Figure 3 shows an example of Doppler velocity estimates from the rotating cylinder phantom using $a = 5$ transmitted angles and $\theta = 5$ degrees. The distribution of velocities clearly reveals the full range of positive and negative particle motion relative to the transducer. These velocities were not corrected for the relative Doppler angle in order to show that the central region of the phantom, where the particles in the phantom are moving normal to the acoustic axis, moves towards zero velocity. The outer edges of the phantom show agreement with the expected value of the maximum velocity. The image also reveals small artifacts in the water region outside of the phantom on either side of the image. This arises from sidelobe artifacts after the beamforming and from the steered plane-wave transmissions which tends to undercover the sides of the images as the steering angle increases. Estimates are most accurate in the central region of the image.

C. Human-subject Scans

Figure 4 shows an example of a normal human-subject scanned in a horizontal plane encompassing the optic nerve and macula. Figure 4a was acquired with $a = 10$ angles and $\theta = 5$ degrees, for 1.25 s, at an effective PRF of 2 kHz. The image represents the average from all of the sliding windows used to estimate velocity versus time and, thus, does not depict blood flow at some instant. Figure 4 b shows a color Doppler image obtained from a single sliding window where $a = 5$ and $\theta = 15$. This example reveals greater detail on a local level such as flow in the choroid and in the fine vessels feeding the retina and choroid. Because flow information was available at every pixel location, spectrograms can be generated over the cardiac cycle at any location of interest. Two spectrograms are shown in Fig. 4 b which clearly reveal flow variation over the cardiac cycle.

IV. Conclusion

Blood flow plays an important role in ophthalmic pathologies such as macular degeneration, glaucoma, tumors, retinopathy of prematurity and vascular malformations. High-speed plane-wave techniques offer a means to produce detailed, quantitative images of ocular

blood flow from the orbit to anterior segment, including optically occult regions of the eye. This information is not available with current ophthalmic imaging devices.

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Fig. 1. Rotation phantom apparatus. A cylinder made with tissue mimicking material containing scattering particles was attached to a DC servo motor and rotated at a constant angular velocity. The probe was aligned normal to the phantom to acquire a circular cross section which yields a range of positive to negative velocities in a single image.

Fig. 2.

Flow moving with a peak velocity of 51.3 mm/s through a 2-mm diameter tube. a) Flow in the plane of the transducer with SVD filter applied. b) Flow through the plane of the transducer without SVD filter applied. Without the SVD filter, the background noise is strong but the region of no flow near the tube wall is clearly visualized. The transducer was tilted 20 degrees relative to the tube.

Fig. 3.

Velocity estimates obtained from a cylindrical phantom rotating at 1 rpm which resulted in a velocity of 31.4 mm/s at the outer edge. The velocities represent the average over the full duration of data collection and have not been corrected for relative Doppler angle.

Fig. 4.

a) Optic nerve head region in a human subject obtained with $a = 10$ and $\theta = 5$. The image depicts the average choroidal perfusion and flow in the short posterior ciliary artery over the full 1.25 s. b) Color Doppler image at one time point showing instantaneous variation of flow in the choroid and in the fine vessels feeding the retina and choroid using $a = 5$ and $\theta = 15$ degrees. Spectrograms are shown for two locations revealing variations in flow and direction over one cardiac cycle.