HHS Public Access

Author manuscript

IEEE Trans Ultrason Ferroelectr Freq Control. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

IEEE Trans Ultrason Ferroelectr Freq Control. 2018 December ; 65(12): 2418–2428. doi:10.1109/TUFFC.2018.2872911.

A Dual-frequency Co-linear Array for Acoustic Angiography in Prostate Cancer Evaluation

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Abstract

Approximately 80% of men who reach 80-years of age will have some form of prostate cancer. The challenge remains to differentiate benign and malignant lesions. Based on recent research, acoustic angiography, a novel contrast-enhanced ultrasound imaging technique, can provide high-resolution visualization of tissue microvasculature and has demonstrated the ability to differentiate vascular characteristics between healthy and tumor tissue in preclinical studies. We hypothesize that transrectal acoustic angiography may enhance the assessment of prostate cancer. In this paper, we describe the development of a dual-frequency, dual-layer co-linear array transducer for transrectal acoustic angiography. The probe consists of 64 transmitting (TX) elements with a center frequency of 3 MHz and 128 receiving (RX) elements with a center frequency of 15 MHz.

Conflict of Interest

P.A.D. declares that he is a co-inventor on a patent describing acoustic angiography and a co-founder of SonoVol, Inc., a company which has licensed this patent.

The dimensions of the array are 18 mm in azimuth and 9 mm in elevation. The pitch is 280 μm for TX elements and 140 μm for RX elements. Pulse-echo tests of TX/RX elements and aperture acoustic field measurements were conducted, and the both results were compared with simulation results. Realtime contrast imaging was performed using a Verasonics system and a tissue-mimicking phantom. Non-linear acoustic responses from microbubble contrast agents at a depth of 35 mm were clearly observed. In-vivo imaging in a rodent model demonstrated the ability to detect individual vessels underneath the skin. These results indicate the potential use of the array described herein for acoustic angiography imaging of prostate tumor and identification of regions of neovascularization for the guidance of prostate biopsies.

I. Introduction

PROSTATE cancer is the most common non-skin cancer and the second leading cause of cancer-related death in men in the United States [1]. Approximately 60-70% of older men display some degree of prostate cancer on autopsy, compared with 15-20% of men who are diagnosed with prostate cancer during their lifetime [2]. Disease management includes active surveillance, radiation therapy, thermal ablation, cryotherapy, hormone therapy, and surgery [3, 4]. In active surveillance, patients are followed by their urologist using periodic physical exams, prostate-specific antigen (PSA) testing, digital rectal exam (DRE), and periodic repeat prostate biopsies [5]. PSA testing is the first step in prostate cancer diagnosis as its levels are often elevated when prostate cancer develops. If cancer is suspected based on initial screening results, more tests will be needed to confirm the diagnosis, including DRE and a prostate biopsy. However, these tests carry their own uncertainties and risks exist. overdiagnosis is considered a major potential drawback of PSA screening and core biopsies are painful, increase the risk of hemorrhage, and provide little confidence that clinically-relevant regions are sampled. As a supplementary modality, transrectal ultrasound (TRUS) has played a substantial role in the diagnosis of prostate cancer due to its ability to provide real-time imaging and biopsy guidance [6]. While TRUS is commonly used for biopsy guidance, B-mode ultrasound exhibits a low sensitivity for locating cancerous regions for biopsy [7].

Recent research has indicated that contrast-enhanced ultra-sound (CEUS) may potentially provide more accurate prostate cancer assessment [7-9]. During expansion of the tumor, new blood vessels will form from pre-existing vessels surrounding the tissue as part of the angiogenic process. Angiogenesis is a well-known hallmark of cancer [10], and is characterized by increased vascular density, vascular tortuosity, vascular malformations, and corresponding changes in blood flow [11, 12]. Previous studies suggested that the presence of these vascular features is correlated with malignancy [13]. Compared to conventional ultrasound, a contrast-enhanced approach can provide an estimate of microvascular perfusion and density. Ultrasound contrast agents (UCAs) (e.g. microbubbles) are used to increase acoustic scattering of blood in vascular spaces and thereby improve imaging of blood flow [14]. Microbubbles are micron-sized gas bubbles that provide enhanced contrast of blood due to the large mismatch in acoustic impedance between the gas core and the surrounding medium, aiding in the identification of blood vessels. During the past decades, a variety of methods have been proposed for contrast agent-specific imaging including, but not

limited to, harmonic imaging [15-17], pulse inversion [18, 19], subharmonic imaging [20], chirp reversal [19] and radial modulation [21]. Although some techniques use the second harmonic signal, it has been noted that the second harmonic can be non-specific to MCAs because tissues also generate second harmonics through nonlinear wave propagation. Recent super-resolution imaging techniques have provided resolution beyond the diffraction limit using microbubble localization techniques [22]. However, this emerging technique requires the acquisition of thousands to tens of thousands of transmit events to generate a single frame.

Recently, our group has investigated an alternative approach to contrast-enhanced ultrasound imaging which relies on the dual-frequency superharmonic ($>3^{\text{rd}}$ harmonics) echoes produced by microbubble contrast agents. Dual-frequency Superharmonic approach allows acquisition of contrast-specific images having high contrast-to-tissue ratio (CTR) without the need to store and process thousands of acquisitions, which is challenging for most current systems. Studies on dual-frequency ultrasound imaging indicate that microbubbles excited with a frequency between 1-5 MHz result in superharmonic echoes from microbubbles which can be detected at frequencies above 15 MHz [23-26]. This method provides unique images of microvessel structure with excellent resolution, thus creating “acoustic angiography” images [27]. As changes in microvascular density and morphology are associated with progression of tumor growth, the ability to image the microvasculature provides additional diagnostic information, which we hypothesize, will improve the sensitivity and specificity of contrast ultrasound to cancer [28-30]. Though superharmonic acoustic angiography cannot match the resolution scale promised by super-resolution imaging, microvessels approximately 200 μm can be imaged with a single transmit event, enabling real-time imaging.

The primary challenge in implementing this imaging technique is presented by the transducer design and fabrication. In superharmonic imaging, separation of transmission and receiving bandwidths is required to ensure high contrast-to-tissue ratio, thus conventional transducer arrays with single center frequencies are not suitable. Compared with the mechanical scanning technique used with previous single-element systems for superharmonic imaging [27], dual-frequency imaging with an array provides increased frame rate, increased depth of field, more precise control over the acoustic pressure field, and also provides opportunities for different imaging modalities [31].

To extend our previous work with a dual-frequency subaperture array [32, 33], a 3 MHz/15 MHz ultrasound array was developed for transrectal dual-frequency acoustic angiography imaging. An array with 64 transmit and 128 receive elements was designed, fabricated and characterized. Pulse-echo tests were conducted for both low and high-frequency elements. The transmitting array was also evaluated by measuring the acoustic pressure profile with a hydrophone. The array transducer's ability to perform superharmonic imaging was tested with a tissue-mimicking phantom by exciting microbubbles flowing through a micro-cellulose tube. Finally, contrast imaging was performed with a multi-channel imaging system in a rat to visualize in-vivo microvasculature.

II. Methods

A. Device development

1) Transducer Design and Fabrication: The dual-frequency transducer array was designed as a dual-layer stacked structure, with a low-frequency transmitting layer and a high-frequency receiving layer (Fig. 1). Structurally, the transmitting (TX) layer was placed below the receiving (RX) layer because the low-frequency transmitted acoustic waves can propagate through the thinner, high-frequency element, but the reverse is not feasible. The placement of the RX layer has little interference on the transmission because of its low thickness ($90\text{ }\mu\text{m}$) compared with the transmitting wavelength ($1300\text{ }\mu\text{m}$). The selection of 3 MHz as the transmitting layer's center frequency was chosen based on the contrast agents' resonant frequency [34]. The high-frequency (15 MHz) receiving layer was positioned on the top of the transducer to share the same acoustic aperture and also minimize the interference from the transmitting layer.

In this stacked structure, two active layers cannot be bonded directly as aliasing echoes generated can shift the resonant frequencies of both layers and decrease the bandwidth. To prevent this, a frequency-selective isolation layer that functions as a quarter wavelength (15 MHz) anti-matching layer was placed in between to isolate the top layer from the bottom layer in the high-frequency mode [35-38]. PZT-5H (CTS 3203HD, CTS Corporation, Elkhart, Indiana, USA) 2-2 composites (ceramic volume ratio 71%) were selected as receiving material for their high coupling coefficients, and PZT-5H ceramics (CTS 3203HD, CTS Corporation, Elkhart, Indiana, USA) were chosen as transmit material for their high dielectric constant and high piezo coefficient.

The array parameters and performance characteristics were considered comprehensively. The number of array elements was determined by the maximum number of input/output channels available on the imaging system electronics. The element pitch was confined by the focal performance, and the total aperture size was determined based on the dimensions necessary for clinical transrectal imaging. In considering anatomy, the prostate is located approximately 10 mm from the rectum. The size of prostate varies naturally with age, potentially increasing further due to benign prostatic hyperplasia (BPH). In general, it is approximately 45 mm in width (maximal transverse diameter), 38 mm in length (the longitudinal diameter as defined by the distance between proximal external sphincter and urinary bladder), and 32 mm in height (maximal anterior-posterior diameter), which means the region of interest is 20-50 mm away from the ultrasound probe [39]. Field II was used to assess a series of designs with varying parameters, and an optimum design with low-frequency and high-frequency elements was ultimately adopted [40, 41]. The details of this configuration are summarized in Table I.

The TX and RX elements are necessary to be physically separated while also having overlapping foci, the array transducer was designed using a stacked configuration with an isolation layer, which the layer also served as the common ground. To improve the transmission sensitivity, light backing (Epo-tek 301) was used for the low-frequency array. Due to the chosen element pitch and aperture design, the piezoelectric layers operated in sliver mode (k33') for low frequency (TX) elements and in 2-2 composites mode for high

frequency (RX) elements. The customized flex circuit consisted of 25 μm -thick copper and a 25 μm polyimide layers. The wavelength of 15 MHz in copper is approximately 310 μm . The copper thickness in the flex circuit is less than $\lambda/10$, thus it does not significantly affect the waveform. In simulation, only the 25 μm polyimide and a 13 μm Parylene layers were considered as matching layers. Since the active material of the RX elements were 2-2 composites (lower impedance compared to PZT ceramics), the two thin polymer layers were expected to decrease the bandwidth. The apertures and matching layers for both TX and RX, as well as the isolation layer were designed using the Krimholtz-Leedom-Matthaei (KLM) model [42]. Material properties of each constitutive component are summarized in Table II.

A prototype of dual-frequency array was then fabricated. First, a PZT plate with thickness of 500 μm (for low-frequency TX) was cleaned and deposited with Ti/Au on both sides. The top electrode was then attached with a layer of conductive epoxy (E-solder 3022, Von Roll Isola, Inc. New Haven, CT), which was cured at room temperature for 24 hours. After curing, the E-solder layer was carefully lapped to a thickness of 30 μm then the RX material, 2-2 composites, was bonded to the TX layer using Epo-Tek 301 (Epoxy Technologies, Billerica, MA), and was then the RX material was lapped to a thickness of 100 μm to achieve a 15 MHz resonance. Finally, the conductive layer composed of Ti/Au was sputtered on the top RX layer.

The flex circuits for both the TX and RX arrays were then bonded to both sides of the stack using Epo-Tek 301. During the flex circuit bonding process, the high frequency and low frequency flex circuits were aligned to ensure the starting elements were at the same position; the high frequency flex circuit was aligned to the 2-2 composites pattern.

After the epoxy was fully cured, a dicing blade (Diamond blade ZH05-DC, DISCO Corporation, Japan) was used to cut the elements with the designated pitch size (280 μm for TX and 140 μm for RX), resulting in a 25 μm kerf. Because it is difficult to maintain stack integrity after fully dicing the top and bottom layers, two different cutting approaches were adopted. First, instead of cutting through the 2-2 composites of the RX element, a partial-depth cutting was used to avoid touching isolation layer. Second, after the dicing process, the array was filled with Epo-tek 301 in a flat fixture to maintain its shape. Both approaches were aimed to hold the transducer in a firm condition but results in an increased level of crosstalk. The cutting depth for TX elements was 500 μm (including 50 μm flex circuit and 450 μm PZT ceramics), and 100 μm for RX elements (including 50 μm flex circuit and 50 μm PZT composites). A layer of parylene was deposited onto the prototype for passivation, with the parylene on the top of the receiving element serving as a matching layer. Finally, the array was interconnected with a printed circuit board for further testing.

2) Transducer Characterization: The electrical impedance magnitude and phase spectra for each TX and RX element were measured using an Agilent 4294A precision impedance analyzer (HP, Palo Alto, CA). For this test, the array was placed in a water tank and the electrical impedance and phase spectra were measured and the element capacitance and dielectric loss at 1 kHz were characterized. Next, pulse-echo testing was conducted to measure sensitivity, center frequency, and bandwidth for each element. A Panametrics 5077PR and a 5900PR pulse/receiver (Panametrics, Inc., Waltham, MA) were used for the

TX and RX impulse tests, respectively. The array was positioned in a degassed/deionized water bath in front of a polished stainless steel plate reflector. The echo response was observed and recorded on an oscilloscope (DSO7104B, Agilent Technologies Inc., Santa Clara, CA). The fast Fourier transform (FFT) function on the oscilloscope was used to determine the frequency response of the acquired RF data. Low-frequency elements were excited with 100 V, and high-frequency elements were excited separately with 1 μ J.

For dual-frequency imaging, the transmitting sensitivity of TX elements is critical. The transmission pressure of TX elements was measured using a calibrated hydrophone (Onda HNA-0400, Onda Co., Sunnyvale, CA, USA) while focusing the array, using all elements, at a depth of 25 mm and 40 mm, respectively. The peak negative pressure was measured to determine the transmission sensitivity. Tests were conducted by applying the highest voltage (approximately 90V) the Verasonics system can provide at the designated frequency to obtain the maximum acoustic field generated by the array.

Insertion loss was measured by exciting a representative array element with a 10-cycle burst and receiving the reflected echo from a polished steel reflector. The received power across a 50- Ω load was referenced to the source power delivered to a 50- Ω reference load and expressed in decibels. The measured value was corrected for loss due to diffraction, attenuation in the water bath, and reflection from the steel target (0.6 dB).

B. Imaging evaluations

1) In-vitro phantom testing: A graphite-gelatin phantom was used for this study. The phantom was composed of 92.5% de-ionized water, 5% n-propanol (to adjust for speed of sound), 2.5% Kodak Photo-Flo 200 (surfactant), 7.5% g/mL porcine gelatin, and 0.115 g/mL graphite. The concentration of graphite was chosen to mimic the experimental attenuation data of the normal human prostate, 0.5 dB/cm/MHz. Contrast agents were poly-disperse (approximately 1 μ m median diameter) lipid coated microbubbles, prepared in-house [43]. A 200 μ m diameter cellulose tube with flowing microbubbles (10^7 microbubbles/mL) was embedded in the phantom at a depth of 35 mm away from the ultrasound probe. A multi-channel research imaging system (Verasonics Vantage 256, Kirkland, WA) was used to drive the array and acquire echoes. For the imaging testing, the array was operated in a mode of single transmit/receive focus linear scan (with focal depth of 35 mm and F# of 2). The TX array beamform 128 lines for each frame and corresponding RX lines were acquired by RX array. Each low-frequency TX element was excited with a one-cycle, 33 V pulse (estimated 1 MPa at focus). High-frequency echoes were filtered with a bandpass filter (9-27 MHz), and time-gain compensation was applied. The array was tested with three scenarios,

- (1) High-frequency B-mode imaging;
- (2) Contrast imaging without microbubbles flowing;
- (3) Contrast imaging with microbubbles flowing.

By combining three images, the array is tested for its capability to perform both B-mode and contrast mode imaging. The array was mounted on a computer-controlled motion stage (Newport, Irvine, CA, USA) and was translated linearly in the elevation direction to form volumetric imaging data set.

2) In-vivo rat imaging: All in-vivo imaging was approved by the University of North Carolina Institutional Animal Care and Use Committee. Fisher 344 rats were anesthetized with isoflurane and then shaved in the lower abdominal/flank region. The transducer was positioned approximately 5 mm from the surface of the animal and was coupled to the skin with ultrasound gel. Before contrast injection, B-mode imaging was performed, followed by contrast mode imaging for baseline measurements. Then, a constant infusion of a 1:1 dilution of contrast to saline was administered, and contrast mode imaging was performed again to detect blood vessels. To increase sensitivity to microbubbles, an excitation voltage of 33V was delivered to elicit higher harmonic tissue responses. A 3D image was acquired with an elevation step size of 0.5 mm. Individual vessels were detected in the 3D pull-back at a depth between 20-30 mm.

III. Results

A. Device development

1) Array transducer design: Fig. 2 shows the predicted pulse-echo response of the co-linear array transducer from KLM model simulations. For TX element, the center frequency was 3.2 MHz, and the -6 dB bandwidth ranged from 2.51 to 3.84 MHz, resulting in a fractional bandwidth of 41%. For the RX element, the center frequency was 15.6 MHz, and the -6 dB bandwidth ranged from 12.6 to 18 MHz, a fractional bandwidth of 30%. These simulation results suggest that with this dual-layer design, a sufficient sensitivity and bandwidth of transmission and receive can be achieved. Fig. 3 shows the acoustic field simulation results for the TX and RX with all elements transmitting to a focal depth of 35 mm. The -6 dB beam widths were $600\text{ }\mu\text{m}$ for TX and $180\text{ }\mu\text{m}$ for RX. Based on this design, the array should be capable of high resolution imaging on both B-mode and contrast mode.

2) Array transducer prototype: A co-linear array prototype was fabricated to evaluate the performance for superharmonic imaging. The active aperture was 9 mm by 18 mm. The total thickness (including flex circuit) was approximately 1 mm. Fig. 4 shows the image of the stacked structure before the element dicing process. Under the microscope, the pattern of the 2-2 composites and the individual layer of TX, RX, and the isolation layer are clearly observed. The flex circuit for both TX and RX elements were designed with an inter-digitated pattern. As shown in Fig. 5 (left), there are 6 PCBs (50 pins for each) connected to the flex circuits (2 for TX elements and 4 for RX elements). The Verasonics Vantage system consists of 2 slots each 128 channels. The connectors TX and RX elements were connected separately through 2 connectors (TX: 64 elements to channels 1-64 on connector 1, RX: 128 elements to channels 129 – 256 on connector 2). After the stacked structure was bonded to the TX and RX flex circuits, the partial-depth dicing process was performed on both top and bottom to form TX and RX elements. Fig. 5 shows the pictures of the prototyped co-linear array transducer. After the PCB bonding to the flex circuit, the array was attached to a customized C-shaped frame in order to perform the phantom and in-vivo testing. As shown in Fig. 5 (middle and right), the transducer was fixed to one end, the flex circuit and PCBs were fixed on an acrylic board. The left figure in Fig. 5 shows the PCBs and their connections with Verasonics system.

3) Characterization of the array transducer: The mean ($\pm$ standard deviation) capacitance of each element in TX elements was 149 ± 12 pF, and dielectric loss was 48 ± 19 mU. The mean capacitance of elements in RX elements was 183 ± 36 pF, and dielectric loss was 116 ± 38 mU. The measured capacitance results of all elements are summarized in Fig. 6. The obtained results showed acceptable dielectric performance, but the loss level was higher than expected and the uniformity was less constant. One of possible reasons is the flex circuit connections. Because the flex circuit was designed in an inter-digitated pattern, the odd and even numbered elements were connected to different circuit boards. From Fig. 6, it was clearly found that the capacitance value of certain part of the high frequency array (elements 30 – 40, 70 – 90) showed different tendencies between odd/even elements. The TX and RX elements exhibit a fundamental resonant frequency of 3.7 MHz and 14.8 MHz, respectively (Fig. 7).

Pulse-echo results of both TX and RX elements are shown in Fig. 8. The average center frequency of the TX elements was measured to be 3.4 ± 0.2 MHz, and -6 dB fractional bandwidth was $36.2 \pm 5\%$. The average center frequency of the RX elements was measured to be 14.8 ± 0.4 MHz and the -6 dB fractional bandwidth was $45.3 \pm 8\%$. Compared to simulations, the RX element showed increased bandwidth, which indicates the isolation layer functions well. This could also be due to the challenge of accurately simulating the 3D behavior of the two stacked arrays using a 1D KLM model. TX elements exhibited high sensitivity but narrow bandwidth due to the light backing design and may be improved by adding a full backing layer in the future.

The insertion losses of the TX and RX elements were calculated from 10 cycle-burst responses as -52 dB and -36 dB, respectively. It was found that the insertion loss of TX elements was relatively low in comparison with the simulation results. This may be due to non-negligible attenuation during wave propagation through the isolation layer and RX elements. Since the TX elements were only used to transmit in contrast imaging mode, the insertion loss should not greatly affect the image quality. Crosstalk measurements indicated satisfactory but not ideal element-to-element isolation. The crosstalk near the center frequency of the array was measured to be -32 dB for TX elements and -28 dB for RX elements between adjacent elements. The results of individual element testing for the completed array are summarized in Table III.

Peak negative pressures produced by the TX aperture were measured at focal depths of 25 mm and 40 mm (Fig. 9). The peak negative pressure at the focus was about 3.5 MPa at the focus of 25 mm and 2.5 MPa at the focus of 40 mm, which is more than sufficient for exciting the superharmonic signal from microbubbles. The mechanical index (MI) can reach >1.5 when focal depth was altered between 20 mm and 40 mm. The beam width (full width at half maximum, FWHM) was measured to be 1.3 mm at the focus of 25 mm and 2.8 mm at the focus of 40 mm.

B. Imaging evaluations

1) In-vitro phantom testing: The phantom image (Fig. 10) shows that the co-linear array was able to detect the microbubble signal flowing in the cellulose tube. The array was tested in 3 scenarios, as described previously. The left figure in Fig. 10 shows high-

frequency B-mode imaging with tissue speckle visible in the image. When operated in contrast mode, speckle signals from the tissue-mimicking material were significantly reduced. When microbubbles were flowing in the tube, the array was able to visualize the signals produced by microbubbles. The full-width half-maximum (FWHM) width of the axial and lateral dimensions were measured to be 400 μm and 200 μm , respectively. The contrast to tissue ratio at 35 mm depth was calculated to be 12 dB.

In imaging testing, several phenomena were observed with increasing TX power: bubble destruction increased with TX power, increasing Contrast to Tissue Ratio (CTR), then tissue harmonics increase at higher TX powers (causing CTR to increase less rapidly), then bubbles are fully destroyed and tissue harmonics continue to increase at the highest TX power (causing CTR to decrease). It was difficult to find an optimal power input/MI to get a bright harmonic signal from the bubbles deep inside the tissue while suppressing tissue harmonics from the region near the transducer surface. MI 0.8 was estimated for the setup in the phantom and in-vivo testing. In the contrast image, some tissue harmonic signals were observed, which can probably be attributed to the nonlinear propagation and transducer's harmonic leakage. As TX power increases, harmonic generation at tissue boundaries and due to propagation increase (tissue with high non-linear coefficient near the transducer). In summary, this testing demonstrates that the array is capable of anatomical tissue imaging and vessel mapping by operating in B-mode and contrast mode. The 3D images acquired using a 3-axis linear motion stage to translate the array in 1-mm increments in the elevation direction are shown in Fig. 11.

2) In-vivo rat imaging: Fig. 12 shows the in vivo experimental setup and results of rat imaging. In the B-mode image (Fig. 12 top-right), the rat skin shows a clear boundary, where CNR was estimated to be 20 dB, and full-width half-maximum (FWHM) width was around 400 μm .

From the contrast mode image with microbubbles (Fig. 12 bottom-right) there is a clear enhancement of microvessels. Combined with the high-frequency B-mode imaging, a pair of acoustic angiography images can be formed. Similar to the volumetric image acquired in the phantom, a 3D image was acquired and reconstructed with an elevation dimension of 0.5 mm step size. Individual vessels were detected in the 3D pull-back at a depth between 20-30 mm (Fig. 13). It was observed that the contrast signal shows a double detection artifact. The high-frequency contrast signal is probably generated by a separate TX cycle or low bandwidth cycle. One possible reason is due to the low transmit bandwidth. This limitation arises from the sacrifice of the light backing design. In future studies, it is proposed to add a backing layer behind the TX elements to enhance the resolution. The other possible reason is due to the Verasonics system. During the transmit beam mapping, a clear high-bandwidth waveform was received by the hydrophone. However, in contrast imaging mode, the wave form became longer. The study of compatibility of this prototype array and the Verasonics system is needed in the near future. Further post-processing and refinement of the bandpass filter on RF line is required to remove residual tissue signal.

IV. Discussion and conclusion

In this work, we developed a co-linear, dual-frequency (3/15 MHz) transducer for demonstrating the feasibility of transrectal acoustic angiography for the first time. The acoustic characterization results indicate that our design concept and technique can achieve fractional bandwidths and transmission/receiving sensitivities for superharmonic microbubble imaging. We used a multi-channel imaging system to demonstrate that the array was capable of inducing higher harmonic response from microbubble contrast agents at a depth of 35 mm in phantom. With a 1-cycle excitation, the target widths in axial and lateral directions were 400 μm and 200 μm , respectively, and CTR was 12 dB. *In-vivo* animal imaging demonstrated the ability to detect individual vessels at a depth of 20 mm.

However, there are several significant limitations of this study. First, based on current results, imaging the entire prostate (38 mm in axial) through the rectal wall (10 mm gap) will be challenging. The width of the image in the lateral direction (18 mm) is limited by current prototype compared with the prostate size (40 mm diameter in transverse direction, though these dimensions increase with age and incidence of BPH [44]). Either mechanical rotation/translation or a phased array beamforming would be required to image the lateral range of the prostate. In future studies, a transducer array with a larger aperture would be desirable for clinical research. In addition, the difference of imaging depth between phantom and in-vivo testing is due to attenuation. In the phantom imaging, the material was uniform and the attenuation is approximately 0.5 dB/MHz/cm. However, for the in-vivo study, both the transmitted wave incident on the blood vessels and the higher-order harmonic wave back to the RX elements must cross through highly-attenuating materials including skin, fat and muscle (2 dB/MHz/cm).

The imaging results showed that the TX array was able to excite the bubbles, and the RX element can capture the non-linear signals. However, in the contrast image, the axial resolution was low due to the low transmit bandwidth. One concern of the array design is from the beam pattern mismatch in elevation between TX and RX arrays. For the TX array, the aperture width is 9 mm in elevation, operated around 3 MHz, with a natural focus ($D^2/4\lambda$) of approximately 40 mm. For the RX array, the aperture width is 6 mm in elevation, operated around 13 MHz, with a natural focus of approximately 76 mm. Thus, the beam width in elevation for TX and RX element are large and difficult to couple to each other. This may explain why the resolution in phantom imaging was good (the vessel is perpendicular to the imaging plane), and the resolution in animal imaging was poor (the vessel tortuosity was more complicated).

There are two potential options: elevation focusing (acoustic lens) can be investigated in further development to improve the coupling between TX and RX. Another option may be advancing current 1-D array to 1.5 D array, which would enable altering the elevation focus in a more dynamic manner.

Nevertheless, these encouraging results indicate that the co-linear array is capable of super harmonic imaging. It holds potential for prostate tumor characterization and identification of regions of neovascularization for biopsy guidance.

Acknowledgment

This work was supported by U.S. Army Medical Research and Materiel Command under the contract PC111309 and by the National Institutes of Health R01EB015508. The authors would like to thank Jianguo Ma, Anthony Novell, K. Heath Martin, Juan Rojas and Wei-Yi Chang for providing instruction and assistance in transducer design, microbubble detection tests, and manuscript preparation.

The authors would like to thank the U.S. Army Medical Research and Materiel Command for providing the funding through the grant PC111309 and the National Institutes of Health through grant R01EB015508.

Biography

Sibbo Li (S'13) received his B.S. degree in mechanical engineering from the University of Science and Technology of China, Hefei, China, in 2008, and his M.S. degree in mechanical engineering from Stevens Institute of Technology, Hoboken, NJ, USA, in 2012. He thereafter joined Dr. Xiaoning Jiang's Group, North Carolina State University, Raleigh, NC, USA and graduated with Ph.D. degree in mechanical engineering in 2017. During his graduate study, his research included array transducer development for microbubble contrast imaging and micromachined piezoelectric composite for high frequency ultrasound. He currently works as a research scientist with Philips Research North America.

Jinwook Kim (S'10–M'17) received the B.S. and M.S. degrees in mechanical engineering from Kyungpook National University, Daegu, South Korea, in 2010 and 2012, respectively. He received the Ph.D. degree in mechanical engineering from the North Carolina State University in 2017, where he was involved in a development of miniaturized ultrasound transducers for acoustic excitation of microbubble contrast agent and microgel drug carriers for diagnostic and therapeutic applications. In 2017, he joined the Joint Department of Biomedical Engineering, The University of North Carolina at Chapel Hill as a Post-Doctoral Research Associate. His current research interests include customizing ultrasound transducers for microbubbles/nanodroplet excitation, IVUS transducers, biosensors, laser ultrasound transducers, imaging system development, and ultrasound signal processing. He serves as a Reviewer of several journals including *Sensors and Actuators A: Physical and Applied Sciences*.

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Fig. 1.

The design of dual-frequency dual-layer co-linear array transducer. The RX and TX elements were designed in a stacked structure. An isolation layer was placed in between to minimize the aliasing echo and to get a good bandwidth of the RX element.

Fig. 2.

The simulation of pulse-echo responses based on the KLM model for TX (left) and RX (right) elements.

Fig. 3.

The simulation of transducer beam profiles using the Field II program. The beam profiles were simulated with a 35-mm focus. (left) Beam profile of the low-frequency TX element without steering. (right) Beam profile of the high-frequency RX element without steering.

Fig. 4.

The stack structure of the dual-layer co-linear array. (left) The top view of the receiving layer (2-2 composites, with 50 μm pillar and 20 μm filler). (right) The side view of receiving layer (PZT 2-2 composites), the isolation layer (E-solder 3022), and the transmit layer (PZT ceramics).

Fig. 5.

The pictures of the dual-layer co-linear array transducer. (middle) A photograph of the array transducer, including the ground wire, array aperture, and flex circuit. (left) A photograph of PCBs and connections with Verasonics system. (right) A photograph of array aperture (before attaching to the frame).

Fig. 6.
Measured dielectric capacitance and loss of TX elements (a) and RX elements (b and c).

Fig. 7.
Measured electrical response of typical transducer element of the TX (top) and RX (bottom) arrays.

Fig. 8.
Measured pulse/echo responses of typical TX (left) and RX (right) element and their FFT spectra.

Fig. 9.

Measured hydrophone results of TX elements acoustic mapping. The pressure mapping (unit: MPa) show two of focal depth, at 25 mm (left) and 40 mm (middle). The measured hydrophone waveform and its FFT spectra (right).

Fig. 10.

Superharmonic image of a cellulose tube filled with microbubbles in the tissue-mimicking phantom, (left) high-frequency B-mode imaging in dynamic range of 40 dB; (center) Contrast imaging without microbubbles flowing in dynamic range of 15 dB; and (right) Contrast imaging with microbubbles flowing in dynamic range of 15 dB

Fig. 11.

The design of a tissue-mimicking phantom for the in-vitro phantom imaging (top-left); a 3D image of phantom test in different modes, high-frequency B-mode (top-right); contrast mode (without microbubble flow, bottom-left); and contrast mode (with bubble flow, bottom-right)

Fig. 12.

The experiment setup of the rat imaging and results. (top-left) The imaging setup (before the probe attached to the rat skin); (top-right) The B-mode imaging of the rat, which imaging plane was also adopted for the contrast imaging; (bottom-left) The contrast imaging without microbubbles flow; and (bottom-right) The contrast imaging with microbubbles flow. (unit: dB)

Fig. 13.
A 3D comparison of B-mode (left) and contrast mode (right) of a rat with clearly identified vessels.

TABLE I

Design parameters of the co-linear array (TX/RX)

Property	Value	
Aperture	9 mm by 18 mm	6 mm by 18 mm
Working mode	Transmitting (TX-3 MHz)	Receiving (RX-15 MHz)
Pitch	280 μm (0.5λ)	140 μm (1.33λ)
Element number	64	128

TABLE II

Material properties of each component of the array

Materials	Layer	Thickness (μm)	Impedance (MRayl)	Longitudinal Velocity(m/s)	Density (kg/m^3)
PZT	TX	500	30	3850	7700
PZT 2-2 composites	RX	100	20	3800	5500
E-Solder 3022	Isolation layer	30	5.5	2110	2590
Parylene	Matching layer	13	3.2	2770	980
Epo-tek 301	Backing layer	-	1.41	1.23	1150

TABLE III

Measured properties for the collinear array (TX/RX)

Property	Value	
Aperture	6mm by 18mm	9mm by 18mm
Working mode	Transmitting (TX-3 MHz)	Receiving (RX-15 MHz)
Pitch size	280 μm (0.5 λ)	140 μm (1.33 λ)
Element number	64	128
Center frequency	3.4 MHz	14.8 MHz
-6 dB fractional bandwidth	36%	45%
Pulse width (-20 dB)	2.7 μs	0.3 μs
Capacitance @ 1 kHz	149 $\pm$ 12pF	183 $\pm$ 36 pf
loss@1 kHz	48 $\pm$ 19 mU	116 $\pm$ 38 mU