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Feasibility of Using Lateral Mode Coupling Method for a Large Scale Ultrasound Phased Array for Noninvasive Transcranial Therapy

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Abstract

A hemispherical-focused, ultrasound phased array was designed and fabricated using 1372 cylindrical piezoelectric transducers that utilize lateral coupling for noninvasive transcranial therapy. The cylindrical transducers allowed the electrical impedance to be reduced by at least an order of magnitude, such that effective operation could be achieved without electronic matching circuits. In addition, the transducer elements generated the maximum acoustic average surface intensity of 27 W/cm². The array, driven at the low (306 kHz) or high frequency (840 kHz), achieved excellent focusing through an ex vivo human skull and an adequate beam steering range for clinical brain treatments. It could electronically steer the ultrasound beam over cylindrical volumes of 100 mm in diameter and 60 mm in height at 306 kHz, and 30-mm in diameter and 30-mm in height at 840 kHz. A scanning laser vibrometer was used to investigate the radial and length mode vibrations of the element. The maximum pressure amplitudes through the skull at the geometric focus were predicted to be 5.5 MPa at 306 kHz and 3.7 MPa at 840 kHz for RF power of 1 W on each element. This is the first study demonstrating the feasibility of using cylindrical transducer elements and lateral coupling in construction of ultrasound phased arrays.

Index Terms

cylindrical transducer; high intensity focused ultrasound (HIFU); scanning laser vibrometer; transcranial phased array

I. Introduction

Therapeutic focused ultrasound has been extensively investigated as a tumor treatment modality over the last several decades. Its potential has been shown in various applications for noninvasive cancer treatments. These include targeted drug delivery [1], tumor tissue ablation [2,3], gene therapy [4,5], and local blood brain barrier (BBB) opening [6-8]. Previous studies have shown that focused ultrasound energy can be delivered through a human skull to the brain to induce tumor tissue destruction [9,10]. However, the skull's presence between the ultrasound beam and a target in the brain causes substantial acoustic energy loss due to its high attenuation and heterogeneity [11]. The skull, due to its complex geometry, severely distorts the propagating ultrasound beam and degrades the focusing quality of an ultrasound transducer.

Transmission of reliable focused ultrasound energy into the brain, without overheating the skull, has been attempted by optimizing the driving frequency of an ultrasound transducer [12,13], using a large scale phased array [10,14-15], operating an ultrasound phased array along with other imaging modalities, and implementing phase and amplitude correction algorithms [15-17]. Most of these studies emphasize that a large scale phased array can maximize energy delivery into a focusing location in the brain. A sufficiently large number of small array elements can precisely control beam steering and focusing by phase and amplitude corrections, while minimizing localized skull heating by propagating the ultrasound beam over most of the skull's surface area.

A low frequency (<500 kHz) ultrasound beam is less sensitive to the irregularity of skull density and thickness, and thus experiences less distortion and diffraction by the skull than a higher frequency (0.5 to 1 MHz) ultrasound beam [13]. This gain comes at a cost of increased focal spot size at lower frequency. The disadvantage of using low frequency ultrasound is that it generates a larger focal volume and a reduced pressure at the focus in contrast to high frequency ultrasound. In addition, ultrasound attenuation in brain tissue is reduced, increasing the possibility of reflections and standing waves which may cause tissue damage outside the focal volume. Although a low frequency may not provide adequate focal gain for thermal surgery, it could be advantageous for gas bubble-enhanced treatments, such as drug delivery and BBB disruption, where small focal spot and high energy are often not needed [18]. A relatively higher frequency may be more suitable for thermal surgery that requires high power and sharp focusing.

In this paper, we describe the design, fabrication, and characterization of a large scale, hemispherical ultrasound phased array with electronic beam steering capability for transcranial ultrasound therapy. The array was constructed using a new transducer manufacturing method that allows reduction of the electrical impedance of a transducer element [19]. We then evaluated the array's element and beam steering capabilities.

II. Materials and Methods

A. Phase Array Construction

We constructed a prototype phased array of 1372 custom-made lead, zirconate titanate (PZT-4) elements (Fig. 1 (a) and (b)). Each element (Fig. 1(a), inset) contained electrodes on its inner and outer surface, and was a cylinder of the following dimensions: 10.0 ± 0.1 mm outer diameter, 6.0 ± 0.2 mm height, and 1.24 ± 0.04 mm wall thickness. The elements were driven at length (and not thickness) mode resonance frequencies. The amplitude of the electrical impedance and phase angle of a single cylindrical PZT array element were measured in degassed, deionized water using a network/spectrum analyzer (HP 4195A, Agilent Technology, Santa Clara, CA, USA). The overall electrical-to-acoustic power conversion efficiency of the element was obtained by using the radiation force measurement technique [20] and scanning laser vibrometer.

An array base frame was constructed from a Lucite hemispherical dome with a 31.8 cm inner diameter and 0.635 cm thickness (Global Plastics Services, Calais, Maine, USA). A 1 mm thick cork-rubber layer was attached to the inside of the hemispherical dome, which served as a low acoustic impedance backing and reduced the wave propagation to the base frame. The manufacturing method had a small impact on the transducer performance. The cork-rubber backed cylindrical transducers had about 4 % wider bandwidth, and the efficiency decreases to approximately 2 % when compared with purely air backed cylindrical transducers. The wave propagation to the Lucite dome through a cork-rubber layer was tested on a cylindrical transducer mounted on the same thickness of a Lucite plate and cork-rubber layer by using a scanning laser vibrometer (PSV-400-M2-20, 20MHz, Polytec, Tustin, CA). The particle

displacement was measured at the boundary between the Lucite plate and cork-rubber layer while the transducer was vibrating. The measurements showed that the propagation of the surface vibration through the cork-rubber layer was less than 10 % of the maximum surface vibration at the front ring surface of the transducer. Therefore, the wave propagation and mechanical crosstalk in the Lucite dome were reduced to avoid any significant mechanical interference during sonication. In addition, the electrical crosstalk was investigated with two cylindrical transducers assembled side by side with 0.5 mm gap. The voltage amplitude and phase changes of the transducer #1 were measured in deionized water while the transducer #2 was sonicated. During the experiment, no power was applied to the transducer #1 while the other transducer was sonicated at 1 W electrical power. The measurement showed no voltage on the transducer #1. It was also verified by the laser vibrometry measurements that no sign of vibration was shown on the transducer #1 while the transducer #2 was sonicated.

The array elements were rigidly mounted on the cork-rubber using an epoxy (301-2, Epoxy Technology®, Billerica, MA, USA). A concentric array pattern, with one center element and 23 rings of elements, was designed to fully utilize the entire inner surface area of the hemispherical dome. The center of the elements in the 23rd ring was located 4 mm below the geometric focus of the base hemisphere (Fig 1(b)). The smallest gaps between the adjacent elements in any direction were less than 0.5 mm. The inner electrode of each PZT element was connected to the signal line with a 2.5 m long coaxial cable (8700, Belden CDT Electronics Division, Richmond, IN, USA), and the ground line was soldered to the electrode on the outer surface. During the experiments, both positive and negative leads were submerged in deionized water with a resistivity higher than 16 M Ω -cm, which provided electrical isolation between the leads. An in-house developed amplifier system with 2000 independent channels [21] was used to drive the array. A 39 cm outer diameter Lucite hemispherical dome was used for an outer casing to protect the cables.

B. Ultrasound Field Measurements

The overall experimental setup is shown in Fig. 2. A 45 $\times$ 50 $\times$ 120 cm³ water tank was lined with anechoic rubber to minimize any acoustic reflections from the tank walls. The tank was filled with degassed, deionized water (*Resistivity* > 16 M Ω -cm), with dissolved oxygen level maintained below 1 ppm. The array was rigidly fastened face-up on the bottom of the tank. The ultrasound pressure field radiating from the array was measured with a 0.2 mm diameter polyvinylidene fluoride (PVDF) needle hydrophone (Precision Acoustics, Dorchester, UK). The hydrophone was affixed parallel to the acoustic axis of the array to a Parker/Velmax 3-D scanning system (Parker, Hannifin, PA, USA; Velmax Inc, Broomfield, NY, USA). A Cartesian coordinate system with its origin the same as the geometric center of the array was established as shown in the upper right hand corner in Fig. 2. The scanned area and step size were controlled by a computer (① in Fig. 2), via a parallel port, using a control program written in LabView (National Instrument, Austin, TX, USA). The radiated pressure field measurements were taken over 20 $\times$ 20 mm² in the XY plane, with the spatial resolution of 0.25 mm at the desired target location. The measurements were captured on a digital oscilloscope (TDS 3012B, Tektronix, Richardson, TX, USA) and saved on the computer via a GPIB bus.

Throughout the experiments, the driving frequency and amplitude of the sinusoidal waveform were identical for all the elements, while the phase was varied for each element to electrically steer the focus. The driving system was controlled by a computer (② in Fig. 2) via a high speed I/O interface board (NI 6534, National Instrument, Austin, TX, USA). In most experiments, a tone burst signal (PRF = 330 kHz, duty cycle = 1%) was used to drive each element. An electrical power of a 0.9 mW/channel was used to measure the radiated fields from

the array when no human skull was present. For transcranial experiments, the electrical power of a 14 mW/channel was applied to the array.

An *ex vivo*, full human calvarium sample, fixed in 10 % buffered formaldehyde, was used to evaluate the transcranial performance of the array. The fixed skull was placed inside the array so that its forehead was fully covered by the elements of the last ring of the array, with the skull top face-down toward the array. The geometric center of the array was approximately 5 cm from the inside surface of the skull top.

C. Scanning Laser Vibrometry Measurements

The particle motion at the surface of an array element in the radial and length directions were qualitatively and quantitatively investigated using a scanning laser vibrometer (PSV-400-M2-20 20MHz, Polytec, Tustin, CA, USA). A 1 mW helium neon (He-Ne) laser light source (wavelength, $\lambda = 633$ nm) produced a spot size of 7 - 25 μm in diameter with micro scan lenses. The vibrometer could measure vibration velocity from 0.02 $\mu\text{m/s}$ to 10 m/s in the frequency range between 0 Hz and 1.5 MHz, and the maximum displacement was ± 75 nm between 30 kHz and 24 MHz, respectively. The vibrometer measured particle velocity of the front and side walls of the array element, in the frequency range between 0.2 MHz and 1 MHz, while the element was sonicated in degassed, deionized water. The laser light was focused on the surface with a 0° incident angle to avoid any error induced by laser light refraction in water.

An experimental setup for the acoustic power measurement radiated from the single array element is shown in Fig. 3. The RF signal to the element was generated by a frequency waveform generator (DS395, Standard Research Systems, Sunnyvale, CA, USA) and amplified with a RF amplifier (ENI Inc, model 240L, Rochester, NY, USA). The array element was fixed at the bottom of the tank filled with degassed, deionized water. The tank was covered with 13 mm thick anechoic rubber (Global Rubber Products, Scarborough, Ontario, Canada) to minimize any acoustic reflections from the tank walls. A tone burst signal (PRF = 1 kHz, duty cycle = 1 %) was used to drive the element. While the transducer was sonicated, the laser beam from the laser sensor head (PSV-400) was directed to the front surface of the element. The laser beam was aligned to be normal to the scanning surface of the element. The transducer surface did not need to be treated by any reflective coatings because the laser beam intensity was high enough to perform the scan over the surface. The particle velocity was used to predict the acoustic power output from the element.

For a parallel comparison with the vibrometry measurements, a single array element was used to measure the electrical-to-acoustic power conversion efficiency in water as described in Reference 20. The array element was placed in a radiation force measurement tank, and an absorbing target facing the transducer was attached to a laboratory balance (AE 200, Mettler Toledo, Columbus, OH, USA). The target was made of 90-mm long flag plastic fibers (Magnolia Brush MFRS Inc., Clarksville, TX, USA) on a 15 mm thick silicon rubber base. The driving RF signal to the array element was generated by a function generator (DS 345, Standard Research Systems, Sunnyvale, CA, USA) and amplified by a 50-dB power amplifier (2100L; ENI, Rochester, NY). The weight changes (Δm) on the balance were stored on the computer at 0.5 sec intervals, before, after and during a 15 sec sonication. The changes (Δm) proportional to the temporal averaged acoustic power (P_A) by the relationship:

$$P_A = (\Delta m g) c \quad (1)$$

where g is 9.8 m/s^2 and c is the speed of sound in water. During sonication, the forward (P_{EF}) and reflected (P_{ER}) electrical powers were measured with a power meter (438A, Hewlett-Packard, Palo Alto, CA, USA). Then, the efficiency (e) was calculated by:

$$e = \frac{P_A}{P_{EF} - P_{ER}} \times 100 \text{ } (\%). \quad (2)$$

D. Hydrophone-assisted phase correction

The primary goal of phase correction is to allow the radiating acoustic waveforms from each element to arrive at desired foci in phase. A simple correction technique was performed to adjust the phase aberrations of the waveforms radiating from each array element at a targeted location. The experimental setup shown in Fig. 2 was used to measure the phase aberration in response to a continuous sinusoidal signal with a known frequency and phase delay. A 0.2 mm in diameter needle hydrophone was used to measure phase aberration in the array. Only one element was driven at a time, and its radiating acoustic waveform was captured by a digital oscilloscope (TDS 3012B, Tektronix, Richardson, TX, USA). Phase correction was performed on the computer (① in Fig. 2) for all array elements and study experiments to eliminate any system induced phase delay and ensure the best possible focusing.

III. Results

A. Resonance frequencies and surface motions of a single cylindrical PZT transducer

In contrast to current transcranial ultrasound technology, our array adopted a recently developed transducer fabrication method [19] that reduces the electrical impedance of the elements, such that it could be driven by a standard driving amplifier without employing a matching circuit. The cylindrical transducer shown in Fig. 4(a) vibrates in the thickness (t), circular (r), and length (l) directions. Assume that the radius (r) of a cylindrical transducer is much greater than its thickness (t); $t \ll r$. The resonance frequencies in the different vibration modes can be predicted with the dimension of the transducer and acoustic material properties of a PZT-4 ceramic [19,22]. The resonance frequencies in the directions of thickness (f_t), circular (f_r), and length motions are predicted to be $f_t = c_{PZT} / (2t)$, $f_r = c_{PZT} / 2\pi r$, and $f_l = c_{PZT} / (2l)$, respectively, where c_{PZT} is the wave propagation speed in a PZT ceramic. Fig. 4 (b) shows an example of the electrical impedance amplitude and phase angle of a single array element measurement. The resonance frequencies of the vibration in the thickness ($f_t=1.62 \text{ MHz}$) and circular ($f_r=129.3 \text{ kHz}$) directions were very different from each other because the thickness of the cylindrical transducer is much smaller than the radius of the transducer.

The resonance frequency in the direction of length, f_l , was measured to be 306 kHz (②). We selected the fundamental frequency at the minimum phase, instead of the minimum impedance. The electrical impedance measured in water at the fundamental frequency ($f_l = 306 \text{ kHz}$) was $121.3 \pm 12.4 \text{ } \Omega$ with a zero phase angle. At the minimum impedance, the phase measurement showed some degree of reactance characteristics. For example, at the first minimum impedance in water, the minimum impedance amplitude and phase were $115.3 \pm 9.2 \text{ } \Omega$ and $-22.4^\circ \pm 3.7^\circ$, respectively. There was a very small difference in the impedance amplitudes between at the minimum phase and at the minimum impedance. However, the phase at the minimum impedance was $-22.4^\circ \pm 3.7^\circ$, which caused the transmitted power loss to the transducer. This accounted for the better efficiency at the minimum phase than at the minimum impedance. This agrees with an earlier report that showed the maximum efficiency of the cylindrical transducers at their phase peak [19]. The second resonance at 840 kHz (③) showed the electric impedance $162.8 \pm 14.7 \text{ } \Omega$ with a phase angle of $-64.2^\circ \pm 4.5^\circ$.

Fig. 5(a) shows the maximum acoustic power outputs and electrical-to-acoustic power conversion efficiencies for the single cylindrical transducer as a function of a peak driving voltage. They were calculated from the particle velocity measurement obtained by the scanning laser vibrometer as the transducer was driven at 306 kHz. The overall electrical-to-acoustic efficiency was 45.29 ± 0.02 %. The inset figures in Fig. 5(a) show the examples of the instantaneous particle velocity profiles across the front surface of the transducer before (①) and after (②) it failed. A maximum acoustic power output of 21.1 W was achieved at the surface of the transducer prior to the failure. The partial failure of the transducer caused the reduction of the maximum acoustic power output. Table 1 shows the overall electrical-to-acoustic power conversion efficiencies of the transducer at 306 kHz and 840 kHz obtained using the radiation force measurement technique. Fig. 5(b) shows the scanning laser vibrometry measurements of the averaged maximum particle displacements on the front surface of the transducer in the frequency range of 200 kHz to 1 MHz. These measurements were obtained by applying 1 W of electrical power to the element. The displacement amplitude peaks were found at 306 kHz and 840 kHz.

Fig 6(a)-(d) show the instantaneous surface displacement profiles of the front surface and side wall of a cylindrical PZT element at 306 kHz and 840 kHz. The front surface motion driven at 840 kHz was similar to motion at 306 kHz. Maximum displacement amplitudes at 1 W electrical power (Fig. 6(e)) were measured to be 51.0 ± 3.4 nm and 9.4 ± 2.1 nm at 306 kHz and 840 kHz, respectively. These maximum particle displacement measurements corresponded to the maximum pressure of a 147.1 kPa at 306 kHz and 74.4 kPa at 840 kHz, respectively, just in front of the transducer by the following [23-25]:

$$P = \rho c (2\pi f d) \quad (3)$$

where P is the pressure, ρ is the density, c is the speed of sound in water, f is the frequency and d is the particle displacement. Assuming the cylindrical transducer has a uniform normal velocity, the acoustic pressure field generated from the transducer can be calculated using the vibrometry displacement measurements over the entire transducer surface. The side wall clearly showed flexural vibration motions in response to the applied sinusoidal signals. The side wall surface vibrated with maximum amplitude of 10.0 ± 0.5 nm and 8.6 ± 0.3 nm at 306 kHz and 840 kHz, respectively.

B. Electronic beam steering and focusing capabilities in water

The sound pressure field measurements at the geometric focus of the hemispherical phased array were taken in the frequency range between 200 kHz and 1 MHz, at a step size of a 10 kHz (Fig. 7). The maximum acoustic pressure amplitude was obtained at 306 kHz, the same frequency as obtained for the length mode resonance of a single cylindrical PZT array element. The second sound pressure peak was found at 840 kHz. The peak pressure amplitude at 840 kHz was reduced approximately 35 % when compared with the one at 306 kHz.

Fig. 8 shows the pressure squared field measurements in water at different focal locations in respect to the geometric focus, $(-30,0,0)$, $(-60,0,0)$, $(0,0,30)$, $(0,0,60)$, and $(0,0,-30)$ mm, when the array was driven at the fundamental frequency. Measurements were normalized to the maximum value in each plot, and showed good electronic beam steering and focusing capabilities of the array over a wide range in the lateral (x- or y-) and axial (z-) directions at the fundamental frequency. Fig. 9 shows the pressure squared field measurements in water at different foci along the lateral (x) and axial (z) direction. The effective beam steering range (50% of the pressure squared amplitude peak), was a 100 mm in the lateral and 60 mm in the depth direction. The focal spot size measured at the full width at half maximum (FWHM) of

pressure squared amplitude at the geometric center was approximately 2.2 mm in diameter and 6.1 mm in length.

Fig. 10 (a)-(c) shows the normalized sound pressure squared amplitude measurements at 840 kHz, with the array focused at the geometric focus, (15,0,0), and (0,0,15) mm. Fig. 10(d) compares the line-scanned, pressure squared amplitude measurements at different focal locations. The effective beam steering ranges was approximately 30 mm in the lateral and 30 mm in the depth direction. The focal spot size at the FWHM of the pressure squared amplitude at the geometric center was approximately 0.7 mm in diameter and 2.3 mm in length.

C. Transcranial beam steering and focusing capabilities

The transcranial beam steering and focusing capabilities were investigated by placing an ex vivo, formaldehyde-fixed full human calvarium sample between the array and hydrophone. Similar to earlier transcranial ultrasound arrays [10,12], our array was a hemisphere phased array with a diameter of 30.4 cm. This allows for the flexibility to locate a patient's head in the array. Each element was phase corrected before the experiments began. Without performing phase correction, the maximum pressure squared amplitude through the skull was 75% lower than the one with phase correction at 306 kHz. In case of driving the array at the high frequency, 840 kHz, the maximum pressure squared amplitude was only 10 % of that with phase correction. Fig. 11(a) shows the comparison between the pressure squared amplitude measurements at the fundamental frequency: in water and with an ex vivo human skull. The pressure squared amplitude peak with the human skull was approximately 25.3 % of the amplitude in water. In a parallel comparison at 840 kHz (Fig. 11(b)), the skull's pressure squared amplitude peak was 5.8 % of that in water.

Fig. 12 shows the normalized, pressure squared field measurements in the xy plane when all elements in the array were driven at 306 kHz and focused at the geometric focus (Fig. 12(a), (b)) and (0,-30,0) mm (Fig. 12(c),(d)). The shapes of the two foci were identical to the ones without the human skull. The FWHM of the pressure squared amplitude in the xy plane was approximately 2.2 mm in diameter for both measurements. The amplitude of the side lobe was approximately 11 % of its pressure squared amplitude peak for both, at the geometric focus and (0,-30,0) mm.

Fig. 13 shows a comparison of the normalized pressure squared field measurements at 306 kHz and 840 kHz, in water and with an ex vivo human calvarium present. With phase correction, identical beam profiles and focal spot sizes were obtained, regardless of the existence of the skull, at 306 kHz and 840 kHz. The significance of the skull-specific phase correction is shown in Fig 13(b, e). At 306 kHz, the ultrasound beam was distorted, and secondary peaks were shown close to the focus. Although the secondary peaks were introduced by the insertion of the skull, the primary peak was clearly shown at the focus. The primary peak was shifted approximately 0.7 mm from the desired focal point. However, without phase correction, there was serious focus destruction at 840 kHz which produced multiple focal spots around the desired focal location.

IV. Discussion

We demonstrated the feasibility of using a new transducer manufacturing method for phased array fabrication. We were able to compensate for phase aberration of the array elements and maximize the contribution of each acoustic element to the production of highly focused acoustic pressures. We simplified the array fabrication process by using a cylindrical PZT transducer as an array element, eliminating the need for impedance matching. This is not typically possible with a small array element since the electrical impedance increases considerably as the element size decreases. In addition, the transducer element generated the

maximum acoustic power of 21 W prior to failure. This translates to an intensity of 27 W/cm² averaged over the whole area of the cylinder diameter. Since each array element was physically separated from its neighboring elements, both the mechanical coupling and electrical crosstalk between the elements were eliminated. Thus, assembly of our 1372 array elements provided precisely-controlled ultrasound beam steering through water.

The phased array was driven at either low (306 kHz) or high (840 kHz) frequency. Driving the array at the lower frequency provided several advantages, including lower phase aberration [13] and higher penetration through the skull [9]. Indeed, the measurements (Figs. 11-12(a-c)) showed lower acoustic field distortion and higher penetration at the low frequency than at the high frequency. The cost of the benefits at the lower frequency was an increased focal spot size. Thus, a low frequency (306 kHz) sonication would be advantageous for treatments where high acoustic energy at the focus was not required. On the other hand, the high frequency (840 kHz) could be used to achieve thermal coagulation requiring sharp focusing to avoid bone heating [10]. Rigorous skull-specific phase correction should be performed to eliminate the phase aberrations caused by the skull. Overall, we showed that our phased array could be used for both low and high frequency applications.

Acoustic field measurements in water indicated that the array could electronically steer the focused ultrasound beam over cylindrical volumes of 100 mm in diameter and 60 mm in height at 306 kHz, and 30 mm in diameter and 30 mm in height at 840 kHz, respectively, without mechanically moving the array. The experiments had *always* been performed in the degassed, deionized water to maintain the array integrity. In a clinical system, the array elements will be coated with a thin layer of insulating material, such as Parylene conformal coating, to provide electrical isolation and improve patient safety. The same steering volumes were obtained with a human skull present. Such a wide steering range at 306 kHz would require only an approximate placement of a patient's head, as the electronic aiming would target the beam to the desired location. In addition, it would allow fast electronic beam steering for advanced multi-location sonication patterns [26]. Compared to the wide beam steering volume at 306 kHz, the steering volume was reduced at 840 kHz, due to decreased wavelength. This was consistent with earlier observations for high frequency phased arrays [12,14].

Transcranial experiments (Fig. 12-13(a-c)) at 306 kHz showed focusing and beam steering capabilities that were similar to the experiments in water, but with beam attenuation. At the fundamental frequency of 306 kHz, the ultrasound beam could be focused without skull-specific phase correction, but with increased beam diameter and side lobes. This result agrees with earlier simulations of low frequency ultrasound beams [13]. Although the ultrasound beams at low frequency experienced less distortion and diffraction while propagating through the skull due to the long wavelength, reverberations in the closed skull cavity may be induced due to the low attenuation of the wave in the brain tissue. This may cause the formation of standing waves and reflections with tissue damage outside the focal spot. Daffertshofer *et al.* [27] reported an unexpected increased rate of cerebral hemorrhages after transcranial thrombolysis treatments at 300 kHz. Azuma *et al.* [28] demonstrated induction of unintentional cavitation due to standing waves in water in ex vivo human cranium. It was reported that the standing wave formation in the transcranial experiments was highly related to the driving frequency and pulse duration at the same acoustic power. Further studies are needed to investigate the role of standing waves in the human skull cavity.

Instituting skull-specific phase corrections restored a sharp focus. Our results showed that, at both the low (306 kHz) and high (840 kHz) frequencies, the acoustic field distortion and focus destruction caused by the skull could be minimized using a phased array with phase correction. This phase correction can be performed by utilizing the skull thickness and density information from CT scans [17,29] as is done in current clinical trials [30].

Using scanning laser vibrometry measurements of a single cylindrical PZT transducer, the maximum pressure amplitude generated at the focus by the array was predicted by solving a simple Rayleigh-Sommerfield integration for the array. As shown in Fig. 6(e), the maximum surface displacements were measured to be, on average, 51 ± 3.4 nm at 306 kHz and 9.4 ± 2.1 nm at 840 kHz, respectively, for an electrical input power of 1 W to the element. Solving a Rayleigh-Sommerfield integration using these displacement measurements, the array would generate maximum pressure amplitudes of 11 MPa at 306 kHz and 15.3 MPa at 840 kHz at the geometric focus, respectively, when there is no human skull present. Using the observations shown in Fig. 11, the maximum pressure amplitude induced through the human skull were predicted to be 5.5 MPa at 306 kHz and 3.7 MPa at 840 kHz at the geometric focus, respectively, when 1 W of RF power was used to drive each element. The effect of nonlinearity in the beam propagation was not taken into account in our estimation. Much higher peak acoustic power can be easily achieved with higher electric power input to the array elements. For example, our measured pressure amplitudes at 1W reported in the study are adequate for blood brain barrier destruction [6-8], thermal coagulation of tissue [10], and thrombolysis [31]. This suggests that our array could be used in both low and high frequency applications for transcranial therapy.

V. Conclusion

This study demonstrated for the first time the feasibility of constructing an electronically steered ultrasound phased array using cylindrical piezoelectric transducer elements and lateral coupling for brain therapy applications. The method allowed the electrical impedance to be reduced by at least one order of magnitude when compared with standard thickness mode operation, such that effective operation could be achieved without electronic matching circuits. The 1372 element array was shown to be sufficient to produce excellent focusing through water and an ex vivo human skull at an adequate beam steering range for clinical brain treatments. The lower frequency (306 kHz) would be suitable for treatments such as focal drug delivery and the higher frequency (840 kHz) for thermal and thrombolytic therapies.

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References

1. Unger EC, McCreery TP, Sweitzer TP, Caldwell VE, Wu Y. Acoustically active lipospheres containing paclitaxel: a new therapeutic ultrasound contrast agent. *Investigate Radiology* 1998;33:886–892.
2. Sibille A, Prat F, Chapelon JY, El Fradil FA, Henry L, Theillier Y, Ponchon T, Cathingnot D. Characterization of extracorporeal ablation of normal and tumor-bearing liver tissue by high intensity focused ultrasound. *Ultrasound Med Biol* 1993;19:803–813. [PubMed: 8134980]
3. Wang Z, Bai J, Du Y, Wen S, Hu K, Xu G, Ma P, Yin N, Chen W, Wu F, Fengt R. Study of a “biological focal region” of high-intensity focused ultrasound. *Ultrasound Med Biol* 2003;29:749–754. [PubMed: 12754074]
4. Greenleaf WJ, Bolander ME, Sarkar G, Goldring MB, Greenleaf JF. Artificial cavitation nuclei significantly enhance acoustically induced cell transfection. *Ultrasound Med Biol* 1998;24:587–595. [PubMed: 9651968]
5. Miller DL, Bao S, Gies RA, Thrall BD. Ultrasonic enhancement of gene transfection in murine melanoma tumors. *Ultrasound Med Biol* 1999;25:1425–1430. [PubMed: 10626630]
6. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. *Radiology* 2001;220(3):640–646. [PubMed: 11526261]

7. Mesiwala AH, Farrell L, Wenzel HJ, Silbergeld DL, Crum LA, Winn HR, Mourad PD. High-intensity focused ultrasound selectively disrupts the blood-brain barrier in vivo. *Ultrasound Med Biol* 2002;28(3):389–400. [PubMed: 11978420]
8. Yang FY, Fu WM, Yang RS, Liou HC, Kang KH, Lin WL. Quantitative evaluation of focused ultrasound with a contrast agent on blood-brain barrier disruption. *Ultrasound Med Biol* 2007;33(9):1421–1427. [PubMed: 17561334]
9. Fry FJ. Transskull transmission of an intense focused ultrasonic beam. *Ultrasound Med Biol* 1977;3:179–184. [PubMed: 595211]
10. Hynynen K, Clement GT, McDoannold N, Vykhodtseva N, King R, White PJ, Vitek S, Jolesz FA. 500-Element Ultrasound Phased Array System for Noninvasive Focal surgery of the brain: A preliminary Rabbit study with ex vivo Human skulls. *Magnetic Resonance in Medicine* 2004;52:100–107. [PubMed: 15236372]
11. Fry FJ, Barger JE. Acoustical properties of the human skull. *J Acoust Soc Am* 1978;63:1576–1590. [PubMed: 690336]
12. Clement GT, Sun J, Giesecke T, Hynynen K. A hemisphere array for non-invasive ultrasound brain therapy and surgery. *Phys Med Biol* 2000;45:3707–3719. [PubMed: 11131194]
13. Yin X, Hynynen K. A numerical study of Transcranial focused ultrasound beam propagation at low frequency. *Phys Med Biol* 2005;50:1821–1836. [PubMed: 15815098]
14. Clement GT, Hynynen K. Investigation of a large-area phased array for focused ultrasound surgery through the skull. *Phys Med Biol* 2000;45:1071–1083. [PubMed: 10795992]
15. Pernot M, Aubry JF, Tanter M, Boch AL, Kujas M, Fink M. High Power transcranial beam steering for ultrasonic brain therapy. *Phys Med Biol* 2003;48:2577–2589. [PubMed: 12974575]
16. Sun J, Hynynen K. The potential of transskull ultrasound therapy and surgery using the maximum available skull surface area. *J Acoust Soc Am* 1999;105:2519–2527. [PubMed: 10212433]
17. Clement GT, Hynynen K. A non-invasive method for focusing ultrasound through the human skull. *Phys Med Biol* 2002;47:1219–1236. [PubMed: 12030552]
18. Hynynen K, McDannold N, Vykhodtseva N, Raymond S, Weissleder R, Jolesz FA, Sheikov N. Focal disruption of the blood-brain barrier due to 260-kHz ultrasound bursts: a method for molecular imaging and targeted drug delivery. *J Neurosurg* 2006;105(3):445–454. [PubMed: 16961141]
19. Hynynen K, Yin J. Lateral mode coupling to reduce the electrical impedance of small elements required for high power ultrasound therapy phased array. *IEEE Trans Ultrason, Ferroelect, Freq Contr* 2009;56:557–564.
20. Hynynen K. Acoustic power calibrations of cylindrical intracavitary ultrasound hyperthermia applicator. *Med Phys* 1993;20:129–134. [PubMed: 8455491]
21. Sokka SD, Juste J, Hynynen K. Design and evaluation of broadband multi-channel ultrasound driving system for large scale therapeutic phased arrays. *IEEE Ultra Symp* 2003:1938–1941.
22. Aronov B. Coupled vibration analysis of the thin-walled cylindrical piezoelectric ceramic transducer. *J Acoust Soc Am* 2009;125:803–818. [PubMed: 19206858]
23. Theobald PD, Robinson SP, Thompson AD, Preston RC, Lepper P, Yuebing W, Swift C, Tyrer J. Fundamental standards for acoustics based on optical methods—Phase two report for sound in water. NPL Report CAIR 3. 2002
24. Theobald PD, Thompson AD, Robinson SP, Preston RC, Lepper P, Yuebing W, Swift C, Tyrer J. Fundamental standards for acoustics based on optical methods—Phase three report for sound in water. NPL Report CAIR 9. 2004
25. Wang Y, Tyrer J, Zhihong P, Shiquan W. Measurement of focused ultrasound fields using a scanning laser vibrometer. *J Acoust Soc Am* 2007;121:2621–2627. [PubMed: 17550161]
26. Daum RD, Hynynen K K. Thermal dose optimization via temporal switching in ultrasound surgery. *IEEE Trans Ultrason, Ferroelect, Freq Contr* 1998;45(1):208–215.
27. Daffertshofer M, Gass A, Ringleb P, Sitzer M, Sliwka U, Els T, Sedlacek O, Koroshetz WJ, Hennerici M. Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia: Increased Risk of Hemorrhage With Combined Ultrasound and Tissue Plasminogen Activator: Results of a Phase II Clinical Trial. *Stroke* 2005;36:1441–1446. [PubMed: 15947262]

28. Azuma T, Kawabata K, Umemura S, OGihra M, Kubota J, Saaaki A, Furuata. Bubble generation by standing wave in water surrounded by Cranium with Transcranial Ultrasonic Beam. *Japanese J Appl Phys* 2005;44:4625–4630.
29. Aubry JF, Tanter M, Pernot M, Thomas JL, Fink M. Experimental demonstration of non invasive transskull adaptive focusing based on prior CT scans. *J Acoust Soc Am* 2003;113:85–93.
30. Hynynen K, Clement G. Clinical applications of focused ultrasound - the brain. *Int J Hyperthermia* 2007;23(2):193–202. [PubMed: 17578343]
31. Behren S, Soengos K, Daffershofer M, Schroeck H, Dempfle CE, Hennerici M. Transcranial Ultrasound-Improved Thrombolysis: Diagnostic VS. Therapeutic Ultrasound. *Ultrasound Med Biol* 2001;27:1683–1689. [PubMed: 11839413]

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Fig 1.

(a) A fully assembled, 1372 element, hemispherical phased array. The inset picture in the upper left corner shows one of the cylindrical, tube-shaped PZT elements, and (b) a cross-sectional view of the array. Each element has a 10 mm outer diameter, 6 mm height, and 1.2 mm wall thickness.

Fig 2.
Experimental setup for a 1372-element, hemispherical ultrasound phased array.

Fig 3.
Schematic diagram of a scanning laser vibrometer experimental setup.

Fig 4.

(a) A simple diagram of a cylindrical PZT transducer, and (b) the typical electrical impedance amplitude and phase measurements of the single cylindrical PZT transducer (10-mm outer diameter and 1.2 mm wall thickness) as a function of frequency. ①: circular mode ($f_r = 129 \text{ kHz}$), ②: length mode ($f_l = 306 \text{ kHz}$), ③: resonance mode ($f_3 = 840 \text{ kHz}$), ④, ⑤, ⑥: complex modes ($f_4 = 1.03 \text{ MHz}$, $f_5 = 1.275 \text{ MHz}$, $f_6 = 1.34 \text{ MHz}$), and ⑦: thickness mode ($f_t = 1.62 \text{ MHz}$).

Fig 5. Scanning laser vibrometry measurements at the front surface of the array element: (a) the maximum acoustic power and electrical-to-acoustic conversion efficiency as a function of peak driving voltage as the transducer is driven at 306 kHz, and (b) maximum particle displacement measurement over the frequency range between 0.2 and 1 MHz.

Fig 6. Instantaneous surface motion profiles of a single cylindrical PZT: front surface motions at 306 kHz (a) and 840 kHz (b), and side wall motions at 306 kHz (c) and 840 kHz (d), respectively. The surface displacement amplitude measurements on the front surface and side wall are shown in (e).

Fig. 7.
Normalized sound pressure field measurements as a function of frequency.

Fig. 8. Normalized sound pressure squared measurement surface plots in the xy plane at different foci: (a) $(0,0,0)$, (b) $(-30,0,0)$, (c) $(-60,0,0)$, (d) $(0,0,30)$, (e) $(0,0,60)$, and (f) $(0,0,-30)$ mm. The array is driven at 306 kHz.

Fig. 9.

The pressure squared field measurements at different foci along the lateral (a) and axial (b) axes in water, without a human skull present. The array is driven at 306 kHz. The measurements are normalized to the maximum amplitude in each plot.

Fig. 10. Normalized sound pressure squared measurements at 840 kHz in the xy plane at different foci: (a) geometric focus, (b) (15,0,0) mm, (c) (0,0,-15) mm. (d) The line-scanned, pressure squared measurements at those three focal locations.

Fig. 11.

Comparison of the sound pressure squared measurements at the geometric focus when the array is driven at either (a) 306 kHz or (b) $f = 840$ kHz in water and with an ex vivo skull present. The measurements are normalized to the maximum amplitude in each plot.

Fig. 12.

Normalized sound pressure squared measurements through an *ex vivo* human skull. The surface plots in the xy plane and line scans along the lateral direction (X axis) show the measurements when the array is focusing at the geometric center (a, b) and $(0, -30, 0)$ mm (c, d). The driving frequency of the array transducer is 306 kHz.

Fig. 13.

Normalized sound pressure squared measurement surface plots in the xy plane at the geometric focus, $(0,0,0)$. The array is driven either at 306 kHz (a-c) and 840 kHz (d-e). The plots are shown the measurements: (a, d) in water, (b, e) with a skull but no phase correction is used, and (c, f) with a skull when phase correction is used.

Electrical-to-Acoustic Conversion Efficiency of the Single Array Element at 306 kHz and 840 kHz Obtained by Using the Radiation Force Measurement Technique [20].

Table 1

driving frequency, $f = 306$ kHz			driving frequency, $f = 840$ kHz		
Electrical Power (W)	Acoustic Power (W)	Efficiency (%)	Electrical Power (W)	Acoustic Power (W)	Efficiency (%)
1.44	0.67	46.48	1.09	0.43	39.15
3.69	1.73	46.98	2.52	0.98	38.89
7.10	3.39	47.72	4.57	1.81	39.60
11.70	5.49	46.97	7.40	2.93	39.59
17.42	8.35	47.92	11.65	4.55	39.06