Title: Temporal and spatial detection of HIFU-induced inertial and hot-vapor cavitation with a diagnostic ultrasound system

Authors: Caleb H. Farny*, R. Glynn Holt†, Ronald A. Roy†

Affiliation: *Department of Radiology, Harvard Medical School, Brigham and Women's Hospital, Boston MA; and †Department of Aerospace and Mechanical Engineering, Boston University, Boston MA

Correspondence: Department of Radiology, Harvard Medical School, Brigham and Women's Hospital, 221 Longwood Ave, Boston MA 02115

Email: cfarny@bwh.harvard.edu

Abstract: The onset and presence of inertial cavitation and near-boiling temperatures in high-intensity focused ultrasound (HIFU) therapy have been identified as important indicators of energy deposition for therapy guidance. Passive cavitation detection is commonly used to detect bubble emissions, where a fixed-focus single-element acoustic transducer is typically employed as a passive cavitation detector (PCD). This technique is sub-optimal for clinical applications, since most PCD transducers are tightly focused and afford limited spatial coverage of the HIFU focal region. A Terason 2000 Ultrasound System was used as a PCD array to expand the spatial detection region for cavitation by operating in passive mode, obtaining the RF signals corresponding to each scan line, and filtering the contribution from scattering of the HIFU signal harmonics. This approach allows for spatially-resolved detection of both inertial and stable cavitation throughout the focal region. Measurements with the PCD array during sonication with a 1.1-MHz HIFU source in tissue phantoms were compared with single-element PCD and thermocouple sensing. Stable cavitation signals at the harmonics and superharmonics increased in a threshold fashion for temperatures above 90 °C, an effect attributed to high vapor pressure in the cavities. Incorporation of these detection techniques in a diagnostic ultrasound platform could result in a powerful tool for improving HIFU guidance and treatment.

Keywords: High intensity focused ultrasound, passive cavitation detection, inertial cavitation, harmonic emissions, boiling

INTRODUCTION

High-intensity focused ultrasound (HIFU) has emerged as a viable treatment modality for a number of different applications, including tumor ablation, hemostasis, thrombolysis and tissue erosion (ter Haar 2004). These applications are thought to rely on the production of heat and/or direct mechanical stress as physical mechanisms to attain successful clinical outcome (Coussios et al. 2007). In addition, bubbles can play a key role in each of these treatments through the production of stable and/or inertial cavitation, as well as outright boiling. In order to understand and monitor the interactive role played by bubbles in these scenarios it is necessary to develop appropriate cavitation sensing techniques. The goal of this study was to evaluate whether a diagnostic ultrasound system equipped with an array transducer could improve spatial sensitivity to cavitation during sonication.

Tumor ablation results from tissue denaturation caused by conversion of HIFU energy into heat via viscothermal absorption of ultrasound. Inertial cavitation has also been implicated in this process. Hynynen (1991) reported elevated temperatures in the presence of inertial cavitation and argued that bubbles were a contributing factor to spatially unpredictable HIFU lesion formation. Lesion deformation due to interaction of the prescribed sound field with bubbles have been noted in numerous studies (Hynynen 1991; Sibille et al. 1993; Watkin et al. 1996) which have recommended that HIFU cancer treatment would be more predictable if cavitation was avoided. Similar results of lesion deformation (Sanghvi et al. 1996; Khokhlova et al. 2006) and additional heating (Lele 1987; Watmough et al. 1993; Clark and ter Haar 1997) have been observed in other studies. More recently, other groups (Holt and Roy 2001; Sokka et al. 2003; Tran et al.

2003; Melodima et al. 2004; Umemura et al. 2005; Coussios et al. 2007) have argued that inertial cavitation can provide a desirable effect owing to the fact that bubble activity can greatly accelerate heating rates, but also recognized that the process must be carefully monitored and controlled.

HIFU has also been used to perform noninvasive hemostasis, primarily in small vessels with diameters up to 5-6 mm or capillary beds (Delon-Martin et al. 1995; Hynynen et al. 1996; Vaezy et al. 1997; Vaezy and Zderic 2007). Cavitation has been thought to assist formation of a homogenate of bio-materials that helps plug bleeding sites (Vaezy et al. 2005). Poliachik et al. (2004) showed that a relative indicator of cavitation dose had a high correlation with platelet aggregation, but it was also found that very high levels of cavitation activity decreased aggregation. Ultrasound in combination with thrombolytic drug therapy has been shown to promote thrombolysis (Francis et al. 1992; Sakharov et al. 2000). Datta et al. (2006) and Prokop et al. (2007) showed that tissue plasminogen activator (t-PA) in the presence of stable cavitation was more effective in clot dissolution than in the presence of inertial cavitation. Thermal ablation, hemostasis and acoustic thrombolysis would be well served by a non-invasive, real-time technique for monitoring both the activity level and type (*i.e.* inertial versus stable) of cavitation induced by ultrasound exposure.

Several methods have been developed to detect bubble activity (ANSI 2007). Passive (Atchley et al. 1988) and active (Roy et al. 1990) cavitation detection techniques take advantage of the acoustical characteristics of inertial and stable cavitation. Both techniques typically employ a single-element focused transducer to improve spatial resolution, although unfocused transducers have also been used for passive cavitation detection (Madanshetty et al. 1991; Zeqiri et al. 2003; Datta et al. 2006; Mast et al. 2008). Two methods have been employed to separate broadband cavitation signals from the scattered HIFU signal. The waveform from the detector may be digitally sampled and post-processed, where cavitation emissions are determined by examining the spectral content (Chen et al. 2003; Rabkin et al. 2005; Mast et al. 2008). A disadvantage to this technique is that the signal can only be monitored intermittently due to the time required to acquire and process the signal. Inertial cavitation may be isolated in real time by employing a passive cavitation detector (PCD) transducer with a sufficiently-high center frequency relative to the HIFU frequency and applying a high-pass filter to remove the energy at the first few HIFU harmonics (Edson 2001; Coussios et al. 2007). A drawback to tightly-focused active and passive cavitation detection is the limited sensing volume. HIFU-induced cavitation evolves both spatially and temporally, so monitoring such a dynamic cavitation field requires a tool that provides greater spatial coverage. This has been accomplished by defocusing the PCD transducer (Datta et al. 2006, Mast et al. 2008) or with multiple focused sensors (Farny et al. 2006).

Increased spatial coverage for cavitation detection has been achieved with standard diagnostic B-mode ultrasound imaging. While its appearance may not represent a direct image of the region of tissue necrosis (Sibille et al. 1993), it has been commonly noted that a hyperechogenic region, or bright spot, appears in the HIFU focal region of the B-mode image acquired immediately following HIFU application (Fry et al. 1970; ter Haar et al. 1989; Fry et al. 1995; Sanghvi et al. 1996; Vaezy et al. 2001; Wu et al. 2004). The bright region is attributed to sound scattering from large gas/vapor bubbles created as the medium heats up (Khokhlova et al. 2006; Coussios et al. 2007). However, active cavitation detection by B-mode ultrasound cannot proceed in real time due to saturation of the signal from the scattered therapy beam, although Vaezy et al. (2001) and Owen et al. (2006) mitigated this problem by interleaving the therapy and diagnostic transducer signals. Nevertheless, strictly simultaneous active cavitation detection cannot be achieved using B-mode imaging technology in a conventional way. Because of this, B-mode hyperechogeneity is indicative of stable gas/vapor bubbles, and not inertial cavitation (Coussios et al. 2007).

Here we describe a novel implementation of B-mode ultrasound sensing technology for spatially- and temporally-resolved detection of both stable and inertial cavitation, as well as a form of non-inertial hot vapor cavitation indicating near-boiling temperatures, during HIFU sonication. A Terason 2000 Ultrasound System, operating in "receive-only mode," was used to detect the broadband signal and scattered field along discrete scan lines. The received RF signal for each scan line was stored and post processed. This beamformed RF signal included broadband energy from inertial collapses and scattering of the HIFU fundamental, harmonics, subharmonics and superharmonics from stable gas/vapor bubbles. This sensitivity to both inertial and stable cavitation, coupled with the ability to resolve the spatially-dependent sound field at video frame rates, yields a potent tool for monitoring cavitation dynamics during sonication.

MATERIALS AND METHODS

The experimental arrangement shown in Fig. 1 was used to expose test samples to high intensity focused ultrasound, measure the temperature elevation resulting from exposure, and to monitor the resulting noise field using two separate passive acoustic sensing arrangements. We investigated HIFU-induced heating at 1.1 MHz using agar-graphite tissue phantoms submerged in a Lucite tank (45 x 45 x 58 cm) filled with degassed, deionized, and filtered water (0.2-µm, Fin-L-Filter). The temperature of the water (22 ± 2 °C) was monitored with an alcohol thermometer daily and the assumed sound speed in the water was adjusted accordingly (Del Grosso and Mader 1972). The samples were supported on a horizontal platform in order to minimize multi-path reflection from boundaries; no attempt was made to eliminate reverberation in the tank proper, as this was deemed insignificant given the dimensions of the tank and the use of focused sources and receivers.

Test samples: tissue phantoms

Agar-based phantoms (Edson 2001; Holt and Roy 2001; Huang et al. 2004) were used to simulate tissue in this study and provided a material in which cavitation and clinical temperature rises could be produced at modest HIFU pressures and for short-duration insonations. Standard cylindrical plastic 35-mm film canisters (31 x 47 mm) were used as molds to cast the phantom.

The submerged test sample was supported from beneath by a horizontal acrylic platform (12 x 5 x 0.5 cm) and positioned lengthwise along the HIFU axis. The platform was mounted to a 3-axis positioned stage for precise alignment of the thermocouple relative to the HIFU focus. A thermocouple (Type E, 125 µm tip diameter, 40 ms response time, ±1.7 °C accuracy, ±0.04 °C precision, Omega, Stamford, CT) was cast into the phantom, with the thermocouple tip positioned 15 ±0.2 mm from the edge of the phantom distal to the HIFU transducer. The position of the embedded thermocouple relative to the transducers was determined by heating the phantom with the HIFU transducer and moving the phantom so as to maximize the temperature rise ($dT < 7$ °C), as well as monitoring the echo off the thermocouple tip from the single-element PCD. Care was taken to reduce self-heating artifacts induced from the thermocouple that could lead to viscous heating from interaction with the sound field (Fry and Fry 1954a,b; Hynynen et al. 1983; Waterman 1990; Waterman et al. 1990). In addition to casting the thermocouple in the phantom to avoid gas entrapment during insertion, the thermocouple had a bare wire tip with a diameter that was smaller than the $\sqrt{\lambda}/5$ criterium suggested by Hynynen and Edwards (1989), where λ is the wavelength, and was aligned parallel to the HIFU acoustic axis.

HIFU Exposure System

We employed a HIFU source consisting of a single-element spherically-focused piezoceramic transducer (focal length = 62 mm; aperture = 70 mm; H-102, Sonic Concepts, Seattle, WA) with a 20-mm diameter hole in the center and a nominal center frequency of 1.1 MHz. A function generator (33120A, Agilent Technologies, Palo Alto, CA) produced the 1.1 MHz drive signal that was subsequently attenuated (-25 dB RF step attenuator, not shown), amplified (60 dB, A-500, ENI, Rochester, NY), and delivered to the sound source via an impedance matching network (Sonic Concepts); the step attenuator was included to increase the range of the input signal amplitude from the function generator into the power amplifier. For purposes of monitoring the focal pressure, the HIFU drive voltage was measured using a high-impedance voltage probe whose output was fed into an RMS-DC converter chip (AD637, Analog Devices, Norwood, MA). The drive voltage exhibited some periodic fluctuation in a manner similar to that described by Thomas et al. (2005), within 2-7% of the initial drive voltage. The signal output from the chip was digitized at 2 kSample/s using an 8-channel signal-conditioning unit (SCXI-1120, National Instruments, Austin, TX) coupled to a 12-bit multi-channel data acquisition board (AT-MIO-16E-1, National Instruments).

The HIFU source pressure was determined via a pressure calibration using a calibrated membrane hydrophone (0.2 mm diameter, model #0200, Precision Acoustics, Dorchester, UK). The focal pressure in the phantom was then inferred by modeling the pressure field with an axisymmetric finite-difference time-domain (FDTD) solution of the Westervelt equation (Edson 2001; Hallaj 1999), using as inputs the source/phantom geometry, measured phantom properties, and source pressure calibration. All exposures consisted of 5.1-s duration continuous wave (CW) insonations.

Passive Cavitation Detection: Single Element Sensor

Inertial cavitation detection was performed using a single-element PCD transducer arrangement similar to previous experiments (Farny et al. 2006). A 15-MHz focused transducer (focal length = 19 mm; aperture = 6.4 mm; -6 dB focal width = 0.62 mm; -6 dB bandwidth = 12–19 MHz; V313, Panametrics-NDT Corp., Waltham, MA) was aligned perpendicular and confocal to the HIFU focus, as shown in Fig. 1. Alignment was achieved by maximizing the signal return from a 3.18-mm diameter brass sphere. In the experiments, the PCD was operated in receive mode and the signal emanating from the HIFU focus was passed through a 50-Ohm power splitter (ZSC 2-2B, Mini-Circuits Lab., NY, NY). One output was directed through a variable attenuator, amplified and filtered by a passive 5 MHz high-pass filter (F5081-FP0-B, Allen Avionics, Mineola, NY) in order to remove the signal energy at the HIFU fundamental, second, third and fourth harmonics. The filtered signal was sent to a broadband RMS-DC converter (AD8361, Analog Devices) and acquired with the signal conditioning unit and data acquisition board described above. This signal provided a measurement of the broadband inertial cavitation emissions from the HIFU focus along with any higher harmonics from the scattered HIFU field as well as super-harmonics from stable cavitation; the broadband emissions dominates this signal at low temperatures (Farny 2007).

The other output from the RF power splitter was passed through an analog 1.1-MHz band-reject filter (Allen Avionics) to remove the fundamental HIFU signal. The signal was sampled with a 14-bit oscilloscope board (CompuScope 14100, Gage Corp., Lockport, IN) at 25 MSamples/s and 5 kSamples per acquisition**.** After acquisition a fast Fourier transform (FFT) of the signal was taken to determine the spectral content. All data acquisition and analysis was performed using MATLAB (R14, The MathWorks, Natick, MA).

Temperature Measurement

The temperature was measured using the thermocouple (described above) aligned parallel to the HIFU transducer axis with its' tip positioned in the focal plane and near the first minimum in the HIFU beam pattern – approximately 0.5 mm off axis – in order to minimize the likelihood of inducing cavitation on the thermocouple surface (Hynynen and Edwards 1989). The signal was acquired using the same signal conditioning unit and data acquisition board described above. The signal was conditioned with a 4 Hz lowpass filter and 60 dB amplifier onboard the SCXI-1120 unit to improve the signal-to-noise ratio.

Passive Cavitation Detection: Array-Based Sensing Using a Diagnostic Imager

The Terason 2000 was equipped with their broadband linear array transducer (10L5, 128 elements, 38 mm aperture) and their Terason system software which was modified to allow access to additional system settings and access to the beamformed RF data. The array axis was aligned parallel to the HIFU transducer axis such that the center element of the array was positioned above the HIFU focus using the same brass target employed for the PCD alignment. The system employs a 64-channel beamformer and the resulting image frame consisted of 128 lines**.** The system assumes a single sound speed for the entire imaging field, the settings of which will be discussed below. The depth of field was set to 8 cm, resulting in a transmit center frequency of 5.8 MHz.

In standard B-Mode, the transducer was driven in the usual way and images were formed based on the backscattered energy. In “PCD mode” the transmit drive voltage was disabled and the “image” thus formed represented the time and space-dependent cavitation emission field along with any HIFU energy scattered into the receiver aperture. Using the manufacturer’s “Ult2matlab_Bmode” software package, the RF data was converted into Matlab format following sonication. The extracted data consisted of time-dependent echo and/or bubble emission voltage for the 128 individual scan lines.

Time base synchronization

The Terason system does not provide a standard trigger for synchronization with the thermocouple and single-element PCD data. A relative time base was established by monitoring the presence of the HIFU signal component in the Terason RF PCD signal (PCD mode), taking into account the 5.1-s sonication duration and the imager frame rate. The images clearly showed when the sonication started and ended.

Acquisition settings

A number of changes to the default image acquisition settings were necessary in order to obtain the bubble emission signals. Many of these changes were made possible through use of a proprietary “Advanced Tools” software package obtained from the manufacturer, which allowed for changes to the transmit/receive modes, assumed sound speed, frame rate and acquisition buffer, focal number, system noise subtraction, absolute time gain compensation (TGC) levels, and apodization window type. Several of the settings employed here were unique to our measurements and differed from the normal mode of operation for a diagnostic ultrasound system; some of these changes are described here, with further details available in (Farny, 2007). In particular, in PCD mode we sought to passively listen to cavitation emission signals, and not to actively scatter off bubbles. Thus, all PCD measurements made during sonication were conducted in a preset acquisition mode for which the transmit signal was disabled on all channels. Following sonication, the transmit signal was then enabled and a standard B-mode image acquired in order to sense the presence of hyperechogenic regions. Sound speed was set to that of the tank water, adjusted for temperature (Del Grosso and Mader 1972). The frame rate, acquisition duration, and receive f-number were 15 Hz, 6.5 s, and unity, respectively. The sampling rate was 24 Msamples/s and the number of samples per RF line, which were dependent on the sound speed *c*, was 2572 samples for *c* = 1491 m/s. No additional averaging or windowing was performed on the RF signals in post processing. The TGC was set to a constant level of 20 dB, which served to maximize signal dynamic range while avoiding clipping. This value was determined by observing the signal scattered by a 3.18-mm diameter brass sphere exposed to HIFU sonication at levels required to generate scattered signals possessing RF voltage amplitudes comparable to inertial cavitation emissions.

System noise subtraction

In order to minimize the impact of electrical noise on the RF signal, the Terason system employs an automated reference frame subtraction process in which the transmit signal is turned off and the resulting acquired signal is used as a measurement of the electrical noise. The electrical noise produced by the system and subsequently detected by the imager is a coherent signal, with a distinct spectrum that exhibits a small fluctuation in amplitude over time scales on the order of several minutes. This noise signal is used as a reference frame, and is subsequently subtracted from the ensuing RF signals to remove the environmental noise. Fluctuation in the background noise is compensated for by obtaining a new reference frame every minute (P. Chang, personal communication). Although the concept of eliminating environmental noise is extremely useful when trying to detect low-amplitude signals, the reference frame was occasionally updated while the bubble emissions were present, thereby removing the signal we sought to detect in the ensuing frames. This problem was circumvented by turning off the reference frame subtraction feature and acquiring a reference frame immediately prior to HIFU sonication. The electrical noise thus acquired was manually removed from the data in post-processing by subtracting the RF signals in the reference frame from the RF signals in all subsequent frames for the given exposure.

Receive frequency response

The receive frequency response of the system was determined by operating the system in pulse-echo mode and reflecting the transmit signal off a water-air interface separated by a thin plastic membrane (department store plastic wrap) in the HIFU water tank. A calibrated capsule hydrophone (HGL-0200, Onda Corp., Sunnyvale, CA) was placed in front of the Terason transducer to measure the transmit waveform, which was digitized by an 8-bit digital oscilloscope (LT264, LeCroy, Chestnut Ridge, NY) and transferred to a PC via the General Purpose Interface Bus (GPIB). The Terason RF echo signal and the hydrophone signal were windowed using a Hanning window. A FFT was performed to obtain the magnitude spectra of the transmit pulse (hydrophone) and the receive echo (Terason). The hydrophone signal was corrected for its frequency calibration. The transmit spectra measured by the hydrophone indicated that the transmit energy was centered about 5.8 MHz, while the backscattered signal off the air-water interface measured by the Terason peaked at 5.2 MHz. This shift is attributed to the imager receive characteristics. The receive amplitude response was obtained by dividing the received signal spectrum by the hydrophone spectrum and normalizing the result, as depicted in Fig. 2. The receive response shows peak sensitivity at 5.2 MHz but also indicates sensitivity to signals centered around 1 and 2.3 MHz.

Beamforming effects

A needle hydrophone (1.0-mm diameter aperture, Dapco, Ridgefield, CT) was driven continuously at 3 MHz (33120A, Agilent Technologies) to simulate a point source to understand beamforming effects imposed by the Terason system in PCD mode. To examine the effects of receive focusing, the hydrophone was positioned opposite of the center array element and moved from 7 – 1 cm in 0.5-cm steps towards the array. Accounting for signal spreading with distance, the array signal amplitude was found to increase with distance until about 4.5 cm, beyond which the amplitude leveled off and remained relatively constant. In order to avoid the region where the receive gain decreased and to ensure that the array did not interfere with the HIFU field the measurement setup was arranged such that the array was positioned 6 cm from HIFU axis.

Using similar sonication parameters the hydrophone was next positioned 6 cm from the array and moved in 1-mm increments parallel to the array. Two aspects of the received signal were of interest. First, although the hydrophone was located at a fixed position, the received peak signal amplitude was not constant over time, an effect attributed to beamforming processing. It was therefore important to determine the extent of the signal amplitude that was constant in time to avoid changes due to beamforming effects and not actual signal fluctuations. Second, it was expected that the beamforming would employ fewer elements near the outer edges of the element array, causing a decrease in signal amplitude. The signal amplitude was found to be relatively constant from 56.6 to 73 mm from the array and from -13 to +12 mm relative to the center element

(0 mm) for the lateral position. The cavitation signals were analyzed over this region. Additionally, the rectangular window was chosen for the apodization in order to produce the narrowest apparent beamwidth from the hydrophone and bubble emissions signals, if present.

SIGNAL PROCESSING

By operating in passive mode and positioning the Terason transducer array parallel to the HIFU transducer axis, time-dependent images of the acoustic emissions along the HIFU acoustic axis were generated such that the HIFU axis resides in the image plane in a constant distance from the array. Accordingly, the HIFU acoustic axis occupies a line in space corresponding to a straight line along the *y*-axis in the images to follow. We expected that the signals generated during sonication and subsequently received by the array could be classified into three categories (Leighton, 1997). The first signal comes from the HIFU fundamental frequency and harmonics that are scattered by graphite particles in the phantom, stable cavitation, and vapor bubbles formed during sonication. Reverberations off other structures present in the tank, as well as direct propagation of the HIFU signal are also likely to be detected. The second signal comes from sub- and super-harmonic emissions generated from stable cavitation, although the sensitivity of the array at the HIFU sub-harmonic frequency was quite low. The third signal will come from broadband acoustic emissions generated by inertial bubble collapses. Inertial cavitation is most likely to occur along the HIFU axis where the pressure is highest in amplitude. For the focal pressures used here and cavitation threshold of these phantoms (~1.6 MPa), the maximum radial extent of the cavitation field was approximately 2 mm, so the radial extent of cavitation relative to the HIFU axis was likely to be relatively low compared to the Terason imaging depth. Thus, inertial cavitation signals were most likely to be produced along a fairly narrow region which is a constant distance from the scan head. For this reason, the TGC levels were set to be constant for the entire depth of field.

The Terason data were analyzed for two types of signals as a function of position and time. The first signal we sought to measure was the broadband emissions from inertial cavitation. Based on the trends seen in previous cavitation measurements (Thomas et al. 2005) the broadband energy was expected to decrease as the tissue phantom heated up. The second signal was that generated by stable cavitation bubbles (sub-harmonic and super-harmonics) and scattering of harmonics of the HIFU field off stable cavitation bubbles and larger vapor bubbles. This signal will be referred to simply as the *harmonic signal* for notational convenience. At a sufficiently-high temperature it was expected that the vapor pressure would approach atmospheric pressure and that large vapor bubbles created in the process would scatter the HIFU signal, such that the amplitude of the harmonic signal would increase over time.

Filtering For Inertial Cavitation Detection

To obtain the broadband signal a FFT was performed on each RF line, where the signal consisted of energy from the scattered HIFU signal (fundamental and higher-order harmonics), stable cavitation (sub- and super-harmonics), and radiated pressure from inertial bubble collapses (broadband). In order to isolate the contribution from inertial cavitation it was necessary to remove the HIFU and stable cavitation signals by digitally filtering the RF signals. One simple method to remove these signals would be to apply a comb filter around each of the harmonic and super-harmonic frequencies, resulting in signal energy only in the unfiltered frequency gaps between the filtered sub/super/harmonic peaks. However, the raw signal in the filtered frequency bands possessed energy from inertial cavitation as well; such an approach would underestimate the contribution from inertial cavitation and reduce the signal-to-noise ratio. Instead, a variation on a standard comb filter was used to set the level of the spectrum in each of the filtered frequency bands equal to the average level of unfiltered spectrum levels just above and below a given filtered band. The assumption is that the frequency dependence of the broadband cavitation emissions does not vary appreciably across a given filtered band. In this manner, the HIFU harmonics and stable cavitation signals were removed from the signal while preserving energy from inertial cavitation emissions.

The filter was applied by taking a ±150 kHz band around each harmonic (nf, for $n = 1, 2, \ldots, 12$ and f is the fundamental frequency) and a ±50 kHz band around each sub- and super-harmonic (where the $n/2$, $\pm n/3$ super-harmonics were considered, for $n = 1, 2, \ldots, 12$), across the entire frequency range. The signals in the intervening bands were windowed and sampled in a random distribution to replace the signal in the adjacent harmonic or super-harmonic band; these sampled signals represented the broadband signal amplitude present in this band in the absence of scattered nonlinear ultrasound and stable cavitation signals. In this manner, the original signal in the intervening bands, assumed to be due to ‘broadband’ signals (i.e., a combination of environmental noise and inertial cavitation, if present) was preserved, and the signal present in the harmonic and superharmonic bands was reduced to the amplitude of the signals in the adjacent band.

The ±150 kHz band was chosen based on experimental observation of the spectra when the HIFU signal was scattered off a spherical target into the linear array, and the ±50 kHz band was based on experimental observation of the spectra in the phantom data; these bandwidths were designed to maximize the ‘broadband’ signal bandwidth while ensuring that the resultant filtered signal did not contain energy from the HIFU or stable cavitation signals. Figure 3 illustrates a typical detected magnitude spectrum before and after application of the broadband comb filter. Note the reduction in signal level at the sub/super-harmonic frequencies following the application of the filter as well as the change in scale of the plots. After the data were filtered an inverse FFT was performed, in order to apply the spatial window described above over which the signal amplitude was relatively constant. The RMS signal level of each RF line was next calculated for comparison with the single-element PCD data.

Filtering For Stable Cavitation Detection

Stable cavitation (including boiling) is characterized not by broadband emissions but rather by the appearance of a combination of sub- and super-harmonic emissions (Leighton, 1997) and scattering of the HIFU fundamental and its harmonics. The stable cavitation signal amplitude was thus obtained by subtracting the broadband spectrum (as described above) from the original measured signal spectrum in order to remove the inertial cavitation signals, if present. The inverse FFT was taken and the data were high-pass filtered above 1.5 MHz using a six-stage Butterworth digital filter to remove the HIFU fundamental signal. Finally, the RMS signal level of each RF line was determined.

RESULTS

A total of 21 phantom measurements (7 with a thermocouple present, 16 without) were performed, where a new phantom was used for each sonication and the focal pressure was approximately 3.5 MPa. Shown here are some characteristic results from three separate measurements to compare the array-based cavitation detection system to the single-element PCD measurements. Figure 4 shows the measurement of the single-element PCD RMS signal and the temperature measured near the focus. The 3.5-MPa focal pressure employed here was sufficiently high so that the onset of inertial cavitation was more or less immediate. The PCD signal decreased over time, in a similar fashion to previous observations. Also present in the PCD signal is an increase in cavitation activity at 2.4 s, most likely due to cavitation on the tip of the thermocouple. The temperature increased until approximately midway through sonication, at which point the thermocouple measured a rapid period of heating before leveling off near the boiling point at about 3.1 s.

The broadband RMS signal detected by the Terason for the same measurement, following post-processing, is shown in Fig. 5. The plot shows elevated signals centered about the HIFU focus that decreased in amplitude further from the focus; these elevated signals are indicative of inertial cavitation activity. Over time, the broadband signal decreased steadily, in agreement with the single-element PCD data in Fig. 4. In addition, the spatial distribution of the bubble activity along the HIFU acoustic axis shifted slightly during sonication. The broadband signals that emanated from the postfocal region appeared to shift towards the focus, as the broadband signals in the postfocal region tended to decrease in amplitude at a faster rate than those in the prefocal region.

Figure 6 shows the RMS signal of the harmonic frequencies over time and along the HIFU axis throughout the focal region for the same exposure. Similar to the broadband measurement, the signal amplitude is highest around the HIFU focus at the start of the sonication, and is most likely due to scattering of the nonlinear harmonic components of the HIFU signal by the graphite particles and sub-resonant-sized bubbles. The amplitude stays relatively constant until about 2.4 s, at which point there is a large increase in the harmonic signal. The high-amplitude signal at 2.4 s coincides with the rapid increase in temperature near the focus to 80 °C and higher. Having surpassed the melting temperature of the phantom (78 °C, Burlew et al. 1980), the high vapor pressure present in the hot molten region promoted the generation of stable cavitation and eventually approached the boiling point; note the large amplitude signals observed in the focal region towards the end of the sonication. The spatial distribution of the harmonic signal showed a different trend in comparison with the broadband signals, as by 4 s the harmonic signal shifted away from the transducer in the postfocal direction.

We quantified the significance of an increase in harmonic scattering with a threshold that was defined by three standard deviations above the mean background signal (Rabkin et al. 2005). The mean background signal and standard deviation was determined from the peak scattered harmonic RMS over the first fifteen frames, equivalent to the first second of sonication. The time window was chosen based on the assumption that the temperature was relatively low for this period ($T < 50$ °C); the signal in this window was assumed to be due to scattering of the HIFU signal off scatterers (both graphite particles and bubbles) in the phantom, representing the background signal when stable cavitation activity was negligible. The harmonic scattering signal within ±0.5

mm of the HIFU focus was analyzed for the time that the threshold was first crossed. Figure 7 shows the threshold time compared with the time that the measured temperature reached 80, 90 and 95 °C in the seven measurements where a thermocouple was present in the phantom. In five out of the seven measurements the temperature corresponding to the threshold time was above 90 °C and in three cases the temperature was above 95 °C; all measurements surpassed 80 °C.

The single-element PCD signal is compared directly to the Terason broadband signal at the focus (z = 0 mm) in Fig. 8, where the Terason signal is from the line corresponding to the focal position. The measurement was performed in a new phantom, where the focal pressure in this experiment was 3.4 MPa and the phantom was not instrumented with a thermocouple. Despite the differences in the signal processing, the two signals agree well, and for low focal pressures where nonlinear effects are minimal and the temperature rise is low, this agreement is to be expected. However, if large, stable vapor-filled bubbles were present in the single-element PCD sensing volume we would expect the signal to contain energy at and above the fifth harmonic, as the single-element PCD signal is conditioned with a 5 MHz high-pass filter. Given the pressure in this phantom, we would expect the temperature to approach boiling, but without a thermocouple it is not possible to comment on the temperatures that were achieved in this exposure.

It is possible, however, to look at the broadband and harmonic images produced from the Terason data, displayed in Figs. 9 and 10a, respectively. The position along the HIFU axis that corresponds to the peak amplitude at the end of the sonication was -3.6 mm for the broadband and -3.3 mm for the harmonic case. In both measurements it is evident that the bulk of the cavitation activity occurred in front of the focus and not in the single-element PCD sensing volume. It is also noted that the region over which inertial cavitation occurred shifted towards the HIFU transducer over time. Thus, it is not surprising that the single-element PCD signal agrees so well with the broadband Terason signal, since there is no significant energy scattered from the harmonics at the focus. More importantly, the Terason data shows significantly more information about the cavitation activity than the single-element PCD, and the comparison between the two detection methods shows the strength of an array-based cavitation detection system. Although no temperature measurement was performed during this measurement, the harmonic scattering threshold was first passed at 1.9 s, suggesting that the temperature in this region was likely above 90 °C; based on the data in Fig. 7, this timescale is feasible.

The appearance of a hyperechogenic region often followed sonication, at which point the array was operated in pulse-echo mode. Figure 10b shows the B-mode image of the phantom acquired from the same data set in Figs. 9 and 10a. The harmonic signal from the Terason measurement during sonication is also displayed. The extent and position of the bright region along the HIFU acoustic axis agreed well with the the region where the high-amplitude harmonic signals appeared. The cause of the hyperechogenic region appearance was further investigated by repeating the experiment in a fresh phantom for a shorter sonication duration of 1.5 s. The peak temperature was 57 °C and no significant increase in harmonic scattering was observed. In addition, there was no evidence of change in the post-sonication B-mode image, a finding that is in accordance with previous experimental observations (Coussios et al. 2007). The agreement seen here provides further evidence that the bright region corresponds to stable cavitation bubbles and large vapor bubbles created at high vapor pressures.

DISCUSSION AND SUMMARY

The results demonstrate that a commercial diagnostic imaging system can be used to apply standard cavitation detection techniques to expand the detection region for both inertial and stable cavitation. Both types of cavitation have been identified as important mechanisms in HIFU energy deposition.

The inertial cavitation activity was found to change both temporally and spatially. Inertial cavitation decreased over time as the temperature near the focus increased, while the distribution of inertial cavitation along the HIFU axis concurrently shifted towards the HIFU transducer. These two effects have been investigated previously (Farny et al. 2006) in a numerical simulation of the bubble dynamics as a function of temperature, and in experimental measurements of broadband emissions as a function of position along the HIFU axis. The simulation indicated that the radiated power from inertial collapses decreased as the medium temperature increased. This effect is attributed to the corresponding elevation in bubble vapor pressure that served to increasingly cushion the bubble collapse and reduce the broadband emissions. This finding is supported by the experimental results presented here. The measurements used two single-element PCDs to simultaneously monitor broadband emissions at the focus and at a prefocal position. Results showed that the prefocal broadband signal increased over time as the broadband signal at the focus decreased, suggesting that bubble activity in the prefocal region was responsible for shielding the sound energy at the focus. Visualization of inertial cavitation throughout the focal region with the technique described here revealed a rather small prefocal shift in inertial cavitation distribution, suggesting that temperature effects on bubble dynamics may play a greater role in decreasing inertial cavitation than prefocal bubble shielding from inertial cavitation.

In contrast with the broadband emissions, the Terason harmonic signal increased as the temperature (measured 0.5 mm lateral to the focus) reached approximately 80 °C. Given a constant driving pressure in a non-perfused and homogeneous medium there are two likely explanations for the increase in the harmonic signal amplitude. In a nuclei-rich and gassy medium, bubbles will grow over time via rectified diffusion, where gas from the surrounding region outside the bubble diffuses into the bubble, causing it to grow (Eller and Flynn 1965). This process is governed largely by bubble size, medium viscosity and driving pressure, and a consistent expansion in the bubble size should be observed over time. However, surface instabilities will eventually cause the bubble to break up, preventing the bubble from growing much larger than resonant size (Yang et al. 2004) and any significant increase in scattering power.

An alternate explanation for an increase in harmonic scattering is bubbles that scatter more effectively because they are larger in comparison to sub-resonant-sized inertial cavitation bubbles, oscillate with a low expansion ratio relative to the driving pressure and persist for much longer timescales. This scenario could be realized by an increase in vapor pressure, a process driven by an increase in temperature. As the temperature passes 78 °C, the phantom melts (Burlew et al. 1980) and the vapor pressure increases towards atmospheric pressure at 100 °C. Such high internal pressures stabilize the bubbles against inertial collapse and breakup from surface instability. These vapor cavities will be very effective at scattering the harmonics of the HIFU drive signal and will also oscillate nonlinearly, resulting in emissions at the harmonics, sub- and super-harmonic frequencies. These combined effects will contribute to the amplitude increase of the harmonic signal shown in Figs. 6 and 10a. While the observation of increased harmonic scattering could be due to growth by rectified diffusion, the agreement observed in Fig. 7 between the harmonic scattering threshold with the high temperatures measured in the phantom suggests that high vapor pressures caused by near-boiling temperatures are the main causes. We refer to this phenomenon as *hot-vapor cavitation*, where the harmonics are scattered by relatively-large bubbles filled primarily with vapor. A rapid increase in temperature would suggest that this effect would behave in a quasi-threshold fashion, as observed in the results, whereas a slower temperature increase towards the boiling point would likely result in a more gradual increase in such scattering effects. Moreover, the development of large vapor bubbles is believed to be the cause of hyperechogenic regions that often appear during sonication and persist up to several minutes afterwards. Further evidence (Coussios et al. 2007; Khokhlova et al. 2006; Rabkin et al. 2006; Rabkin et al. 2005; Vaezy et al. 2001) that hyperechogenic regions are caused by hot-vapor cavitation, not necessarily inertial cavitation, is bolstered by the correlation of the position and length of the hyperechogenic region to the harmonic scattering region. The cause of hyperechogenicity is important, since its appearance and extent has been used as an indication of a therapeutic effect (Illing et al. 2006), and it is likely that tissue necrosis will have already been achieved by the time boiling has occurred.

The application of passive cavitation detection techniques in an imaging array is a natural extension of a single-element PCD, given the option to acquire and process the RF signals, and the result is an improved method for observing cavitation dynamics. There are several limitations to this approach, however. Currently, this technique cannot be used for real-time imaging and the current setup only allows a relative timebase to be established, in the absence of a trigger. In addition, the acquisition and processing time inherent in the multi-element imaging system makes it difficult to measure cavitation dynamics in the presence of a lower duty cycle or situations where cavitation is sporadic and higher acquisition rates are required. However, the frame acquisition rate is similar to typical active and passive cavitation detection setups where the waveform is digitally sampled and saved to a computer.

The signal from stable cavitation and the HIFU source scattered in the phantom overlaps with the broadband signals from inertial cavitation. The broadband comb filter assumes that the broadband signal that is used to replace the harmonic signals is representative of the broadband signal that would be present in the absence of the harmonic signals. The bandwidths that were chosen for the filter were related to the bandwidth of the HIFU source and were based on experimental observation of the bandwidth of the super-harmonic signals. The entire spectrum was filtered to obtain the inertial cavitation signal as opposed to detection of the broadband signal over a narrow band between adjacent harmonics (Chen et al. 2003) in order to increase the signal-to-noise ratio (on the order of 2-3 dB). While this approach assumes that the broadband signals can be extrapolated to the adjacent frequency band, the method resulted in a small but distinguishable increase in signal; the resulting space- and time-dependent signal appeared otherwise similar when the harmonic and super-harmonic bands were simply nulled. Ideally, the signal would not have been beamformed, so that cropping the time-resolved signal following the filter step would not have been necessary. This scenario would simplify the analysis by removing the need to perform the inverse Fourier transform.

The signal processing techniques described here were necessary for detection of inertial cavitation. Detection of the scattered harmonic signal, however, was only moderately enhanced by the application of the comb filter. Given the Terason transducer frequency response, the strongest harmonic signals that were detected, aside from the 1.1-MHz signal, were the signals from the second, fourth and fifth harmonics, and generally a plot of the RMS signal level following the 1.5-MHz digital high-pass filter revealed emergence of the scattered harmonic signature without the aid of the broadband signal subtraction (although the signal-to-noise ratio benefited from the subtraction of the broadband signal). Monitoring the real-time, unfiltered B-mode image showed a very noisy signal, but there was a defined bright signal region from the focus which visibly narrowed in width when temperatures reached 80 – 90 °C. Thus, implementation of an in-line analog or digital high-pass filter could provide real-time hot-vapor cavitation detection. Many diagnostic ultrasound systems possess in-line filtering (Szabo 2004), so the techniques described here may be feasible to implement in real-time.

A spatially- and temporally-resolved system that is inherently co-registered with B-mode imaging and can detect the presence of large vapor bubbles and distribution of inertial cavitation activity can provide a helpful tool for informing both clinical treatment scenarios and basic research on spatially-dependent cavitation effects. The unpredictability of the onset of cavitation and the associated thermal and mechanical effects makes it important to detect cavitation with a higher temporal resolution than current clinical techniques. The ability to determine the onset of hot-vapor cavitation also provides a powerful, noninvasive method for obtaining a reference point for the temperature and treatment status. Finally, these methods may be easily extended to other therapeutic ultrasound applications that are affected by cavitation, where interpretation of the bubble signals may be dependent on a given effect, such as nonthermal mechanical cavitation effects.

Acknowledgements – The authors would like to thank Drs. Robin Cleveland and Peter Chang for their assistance in the characterization of the Terason system and Dr. Thomas Szabo for helpful discussions on diagnostic ultrasound imaging. The authors gratefully acknowledge support from The Gordon Center for Subsurface Sensing and Imaging Systems via NSF award number EEC-9986821 and the U.S. Army, Award Number DAMD17-02-2-0014 (The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014). The content of the information in this paper does not necessarily reflect the position or the policy of the Government.

REFERENCES

ANSI Technical Report—Bubble detection and cavitation monitoring. ANSI 2007; S1.24:TR-2002.

Atchley AA, Frizzell LA, Apfel RE, Holland CK, Madanshetty S, Roy RA. Thresholds for cavitation produced in water by pulsed ultrasound. Ultrasonics 1988;26:280-285.

Burlew MM, Madsen EL, Zagzebski JA, Banjavic RA, Sum SW. A new ultrasound tissue-equivalent material. Radiology 1980;134:517-520.

Chen WS, Brayman AA, Matula TJ, Crum LA. Inertial cavitation dose and hemolysis produced in vitro with or without Optison. Ultrasound Med Biol 2003;29:725-737.

Clark RL, ter Haar GR. Temperature rise recorded during lesion formation by high-intensity focused ultrasound. Ultrasound Med Biol 1997;23:299-306.

Coussios CC, Farny CH, ter Haar G, Roy RA. Role of acoustic cavitation in the delivery and monitoring of cancer treatment by high-intensity focused ultrasound (HIFU). Int J Hyperthermia 2007;23:105-120.

Datta S, Coussios CC, McAdory LE, Tan J, Porter T, de Courten-Myers G, Holland CK. Correlation of cavitation with ultrasound enhancement of thrombolysis. Ultrasound Med Biol 2006;32:1257-1267.

Del Grosso VA, Mader CW. Speed of sound in pure water. J Acoust Soc Am 1972;52:1442-1446.

Delon-Martin C, Vogt C, Chignier E, Guers C, Chapelon JY, Cathignol D. Venous thrombosis generation by means of high-intensity focused ultrasound. Ultrasound Med Biol 1995;21:113-119.

Edson PL. The role of acoustic cavitation in enhanced ultrasound-induced heating in a tissue-mimicking phantom. Unpublished doctoral dissertation, Department of Aerospace and Mechanical Engineering. Boston, Boston University. 2001.

Eller A, Flynn HG. Rectified diffusion during nonlinear pulsations of cavitation bubbles. J Acoust Soc Am 1965;37:493-503.

Farny CH. Identifying and monitoring the roles of cavitation in heating from high-intensity focused ultrasound. Unpublished doctoral dissertation, Department of Aerospace and Mechanical Engineering. Boston, Boston University, 2007.

Farny CH, Holt RG, Roy RA. Monitoring the development of HIFU-induced cavitation activity. Proceedings of the 5th International Symposium on Therapeutic Ultrasound, Boston, MA, American Institute of Physics, 2006;348-352.

Francis CW, Onundarson PT, Carstensen EL, Blinc A, Meltzer RS, Schwarz K, Marder VJ. Enhancement of fibrinolysis in vitro by ultrasound. J Clin Invest 1992;90:2063-2068.

Fry WJ, Fry RB. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes—Experiment. J Acoust Soc Am 1954;26;311-317.

Fry WJ, Fry RB. Determination of absolute sound levels and acoustic absorption coefficients by thermocouple probes—Theory. J Acoust Soc Am 1954;266;294-310.

Fry F, Heimburger RF, Gibbons LV, Eggleton RC. Ultrasound for visualization and modification of brain tissue. IEEE Transactions on Sonics and Ultrasonics 1970;SU-17:165-169.

Fry FJ, Sanghvi NT, Foster RS, Bihrle R, Hennige C. Ultrasound and microbubbles: their generation, detection and potential utilization in tissue and organ therapy-Experimental. Ultrasound Med Biol 1995;21:1227-1237.

Hallaj IM. Nonlinear acoustics in underwater and biomedical applications: Array performance degradation and time reversal invariance. Unpublished doctoral dissertation, Electrical Engineering. Seattle, WA, University of Washington, 1999.

Holt RG, Roy RA. Measurements of bubble-enhanced heating from focused, MHz-frequency ultrasound in a tissue-mimicking material. Ultrasound Med Biol 2001; 27:1399-1412.

Huang J, Holt RG, Cleveland RO, Roy RA. Experimental validation of a tractable numerical model for focused ultrasound heating in flow-through tissue phantoms. J Acoust Soc Am 2004;116:2451-2458.

Hynynen K, Martin CJ, Watmough DJ, Mallard JR. Errors in temperature measurement by thermocouple probes during ultrasound induced hyperthermia. Brit J Radiol 1983;56;969-970.

Hynynen K, Edwards DK. Temperature measurements during ultrasound hyperthermia. Med Phys 1989;16;618-626.

Hynynen K. The threshold for thermally significant cavitation in dog's thigh muscle in vivo. Ultrasound Med Biol 1991;17:157-169.

Hynynen K, Colucci V, Chung A, Jolesz F. Noninvasive arterial occlusion using MRI-guided focused ultrasound. Ultrasound Med Biol 1996;22:1071-1077.

Illing RO, Leslie TA, Kennedy JE, Calleary JG, Ogden CW, Emberton M. Visually directed high-intensity focused ultrasound for organ-confined prostate cancer: a proposed standard for the conduct of therapy. Brit J Urol Int 2006;98:1187-1192.

Khokhlova VA, Bailey MR, Reed JA, Cunitz BW, Kaczkowski PJ, Crum LA. Effects of nonlinear propagation, cavitation, and boiling in lesion formation by high intensity focused ultrasound in a gel phantom. J Acoust Soc Am 2006;119:1834-48.

Lele PP. Effects of ultrasound on solid mammalian tissues and tumors in vivo. In: Repacholi MH, Grandolfo M, Rindi A, eds. Ultrasound: Medical applications, biological effects and hazard potential. New York: Plenum, 1987:275-306.

Leighton TG. The Acoustic Bubble. San Diego, CA, Academic Press, Inc. 1997.

Mast TD, Salgaonkar VA, Karunakaran C, Besse JA, Datta S, Holland CK. Acoustic emissions during 3.1 MHz ultrasound bulk ablation in vitro. Ultrasound Med Biol, in press.

Madanshetty SI, Roy RA, Apfel RE. Acoustic microcavitation: its active and passive acoustic detection. J Acoust Soc Am 1991;90:1515-1526.

Melodima D, Chapelon JY, Theillere Y, Cathignol D. Combination of thermal and cavitation effects to generate deep lesions with an endocavitary applicator using a plane transducer: Ex vivo studies. Ultrasound Med Biol 2004;30:103-111.

Owen NR, Bailey MR, Hossack J, Crum LA. A method to synchronize high-intensity, focused ultrasound with an arbitrary ultrasound imager. IEEE Trans Ultrason Ferroelectr Freq Contr 2006;53:645-650.

Poliachik SL, Chandler WL, Ollos RJ, Bailey MR, Crum LA. The relation between cavitation and platelet aggregation during exposure to high-intensity focused ultrasound. Ultrasound Med Biol 2004;30:261-269.

Prokop A, Soltani A, Roy RA. Cavitational mechanisms in ultrasound-accelerated fibrinolysis. Ultrasound Med Biol 2007;33:924-933.

Rabkin BA, Zderic V, Vaezy S. Hyperecho in ultrasound images of HIFU therapy: Involvement of cavitation. Ultrasound Med Biol 2005;31:947-956.

Rabkin BA, Zderic V, Crum LA, Vaezy S. Biological and physical mechanisms of HIFU-induced hyperecho in ultrasound images. Ultrasound Med Biol 2006;32:1721-1729.

Roy RA, Madanshetty SI, Apfel RE. An acoustic backscattering technique for the detection of transient cavitation produced by microsecond pulses of ultrasound. J Acoust Soc Am 1990;87:2451-2458.

Sakharov DV, Hekkenberg RT, Rijken DC. Acceleration of fibrinolysis by high-frequency ultrasound: The contribution of acoustic streaming and temperature rise. Thromb Res 2000;100:333-340.

Sanghvi NT, Fry FJ, Bihrle R, Foster RS, Phillips MH, Syrus J, Zaitsev AV, Hennige CW. Noninvasive surgery of prostate tissue by high-intensity focused ultrasound. IEEE Trans Ultrason Ferroelectr Freq Contr 1996;43:1099-1110.

Sibille A, Prat F, Chapelon JY, Abouelfadil F, Henry L, Theilliere Y, Ponchon T, Cathignol D. Characterization of extracorporeal ablation of normal and tumor-bearing liver tissue by high-intensity focused ultrasound. Ultrasound Med Biol 1993;19:803-813.

Sokka SD, King R, Hynynen K. MRI-guided gas bubble enhanced ultrasound heating in in vivo rabbit thigh. Phys Med Biol 2003;48:223-241.

Szabo TL. Diagnostic Ultrasound Imaging: Inside Out. Burlington, MA, Elsevier Academic Press, 2004.

ter Haar GR, Sinnett D, Rivens I. High intensity focused ultrasound--a surgical technique for the treatment of discrete liver tumors. Phys Med Biol 1989;34:1743-1750.

ter Haar GR. Therapeutic and surgical applications, in Physical Principles of Medical Ultrasonics, 2nd ed. Hill C, Bamber JC, ter Haar GR. Chichester UK, Wiley & Sons: 407-456, 2004.

Thomas CR, Farny CH, Coussios CC, Roy RA, Holt RG. Dynamics and control of cavitation during high-intensity focused ultrasound application. Acoust Res Lett Online 2005;6:182-187.

Tran BC, Seo J, Hall TL, Fowlkes JB, Cain CA. Microbubble-enhanced cavitation for noninvasive ultrasound surgery. IEEE Trans Ultrason Ferroelectr Freq Contr 2003;50:1296-1304.

Umemura S, Kawabata K, Sasaki K. In vivo acceleration of ultrasonic tissue heating by microbubble agent. IEEE Trans Ultrason Ferroelectr Freq Contr 2005;52:1690-1698.

Vaezy S, Martin R, Schmiedl U, Caps M, Taylor S, Beach K, Carter S, Kaczkowski P, Keilman G, Helton S, Chandler W, Mourad P, Rice M, Roy R, Crum L. Liver hemostasis using high-intensity focused ultrasound. Ultrasound Med Biol 1997;23:1413-1420.

Vaezy S, Shi X, Martin RW, Chi E, Nelson PI, Bailey MR, Crum LA. Real-time visualization of high-intensity focused ultrasound treatment using ultrasound imaging. Ultrasound Med Biol 2001;27:33-42.

Vaezy S, Vaezy S, Starr F, Chi E, Cornejo C, Crum L, Martin RW. Intra-operative acoustic hemostasis of liver: production of a homogenate for effective treatment. Ultrasonics 2005;43:265-269.

Vaezy S, Zderic V. Hemorrhage control using high intensity focused ultrasound. Int J Hyperthermia 2007;23:203-211.

Waterman FM. Determination of the temperature artifact during ultrasound hyperthermia. Int J Hyperthermia 1990;6:131-142.

Waterman FM, Nerlinger RE, Leeper JB. Catheter induced temperature artifacts in ultrasound hyperthermia. Int J Hyperthermia 1990;6;371-381.

Watkin NA, ter Haar GR, Rivens I. The intensity dependence of the site of maximal energy deposition in focused ultrasound surgery. Ultrasound Med Biol 1996;22: 483-491.

Watmough DJ, Lakshmi R, Ghezzi F, Quan KM, Watmough JA, Khizhnyak E, Pashovkin TN, Sarvazyan AP. The effect of gas bubbles on the production of ultrasound hyperthermia at 0.75 MHz: A phantom study. Ultrasound Med Biol 1993;19:231-241.

Wu F, Wang ZB, Chen WZ, Zou JZ, Bai J, Zhu H, Li KQ, Xie FL, Jin CB, Su HB, Gao GW. Extracorporeal focused ultrasound surgery for treatment of human solid carcinomas: Early Chinese clinical experience. Ultrasound Med Biol 2004;30:245-260.

Yang X, Roy RA, Holt RG. Bubble dynamics and size distributions during focused ultrasound insonation. J Acoust Soc Am 2004;116:3423-3431.

Zeqiri B, Gelat PN, Hodnett M, Lee ND. A novel sensor for monitoring acoustic cavitation. Part I: Concept, theory, and prototype development. IEEE Trans Ultrason Ferroelectr Freq Contr 2003;50:1342-1350.

Figure Captions

Figure 1: Experimental arrangement used in the Terason cavitation emission imaging experiments.

Figure 2: Normalized Terason magnitude response in receive mode.

Figure 3: Terason signal a) before and b) after the broadband comb filter was applied. The dotted lines indicate the frequencies that corresponded to the harmonics that were filtered. The data was obtained in an agar-graphite phantom exposed to 5.1 s of CW 1.1 MHz sound energy at a pressure amplitude of 2.5 MPa.

Figure 4: High-pass-filtered RMS PCD signal and temperature measured in an agar-graphite phantom. The thermocouple tip was positioned 0.5 mm lateral to the HIFU focus and the HIFU transducer was operated at a 3.5-MPa focal pressure continuously for 5.1 s.

Figure 5: Terason RMS broadband signal following the broadband comb filter for the same data set shown in Fig. 4.

Figure 6: Terason RMS scattered harmonic signal, following subtraction of the broadband signal and filtering of the HIFU signal, for the same data set as shown in Figs. 4 and 5.

Figure 7: The time per measurement that the thermocouple registered 80, 90 and 95 °C compared with the time the scattered harmonic signal significantly increased above the background scattered harmonic signal. The threshold for this signal increase is defined as three standard deviations above the mean peak signal over the first second of sonication.

Figure 8: Comparison of the single-element PCD signal as a function of time with the broadband-filtered Terason signal from the array line corresponding to the focus. The single-element PCD focus was positioned to be sensitive to the HIFU focus (0 mm). The focal pressure was 3.4 MPa.

Figure 9: The broadband signal processed from the Terason data as a function of time and position relative to the HIFU focus. The data is from the same data set as Fig. 8.

Figure 10: (a) The scattered harmonic signal processed from the Terason data as a function of time and position relative to the HIFU focus. The data is from the same experiment as shown in Fig. 9. (b) The hyperechogenic region measured in pulse-echo mode after sonication for the same experiment. The arrows in each image denote the extent of the appearance of vapor bubbles.