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Dynamics and control of cavitation during high-intensity focused ultrasound application

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Abstract: In this paper the results of two studies related to high-intensity focused ultrasound (HIFU) and cavitation are reported. The first study described used polyacrylamide phantoms to gain insight into the behavior of cavitation activity in the focal region of the HIFU transducer. Results indicate that cavitation is the source of a previously observed enhanced heating effect in HIFU. The second study discussed used agar-graphite phantoms to see if changing the duty cycle of the driving could effect some measure of control over the cavitation activity; the results indicate that it can.

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1. Introduction

Above a certain critical acoustic pressure threshold, the temperature rise measured near the focus of a high-intensity focused ultrasound (HIFU) source in a tissue-mimicking phantom behaves much differently than below this threshold. It has been shown that the change in behavior can be attributed to inertial cavitation activity[1–3]—the bubbles act as an additional heat source[2] in two ways: (1) they radiate broadband acoustic emissions that are readily absorbed by the medium and (2) shearing stress converts fluid flow to heat in a viscous boundary layer near the bubble wall. This "enhanced heating" effect has also been observed *in vivo*.[4]

In addition, cavitation bubbles have recently proven useful in a number of different ways: creating larger and deeper lesions,[5] as tissue ablators,[6,7] and as image enhancers during HIFU application.[8] Although cavitation has been shown to be beneficial, if it is initiated in the wrong region or allowed to develop out of control, it can cause irreversible damage to healthy tissue. In light of this fact, it is essential that the cavitation behavior be well understood, and if possible, controlled. Here, "control" implies a control of the spatial and temporal evolution of the bubble field, resulting in sustained bubble-enhanced heating over a well-defined volume.

In this paper, we present results from experiments designed to observe cavitation in optically transparent tissue phantoms with video imaging and experiments designed to gain a degree of control over the cavitation field.

2. Experimental methods

Two independent experimental setups were used to collect the data presented in this paper. One was used for the video imaging (VI) experiments, and the other for the cavitation control (CC) experiments. The two apparatus were built similarly enough so that a single schematic (Fig. 1) can be used to represent both.

The HIFU source (Sonic Concepts, H201, H102) (Ref. 9) was driven by an amplifier (ENI 150, ENI A-500), whose input signal (2.0 MHz for the VI study, and 1.1 MHz for the CC study) was provided by a function generator (HP8116A, HP33120A). The amplifier output impedance was matched to the HIFU source via a matching network provided by the manufacturer of the HIFU source transducers. The PCD transducer (Panametrics, V313) was a 15-MHz, single-element focused piezo-electric receiver. The signal from the PCD transducer was high-pass filtered (cutoff frequency 5 MHz; Allen Avionics, F508-5PO-B), amplified[9] and input to a peak detector (Panametrics, PDM-2, 5607UA) whose output was recorded by a data

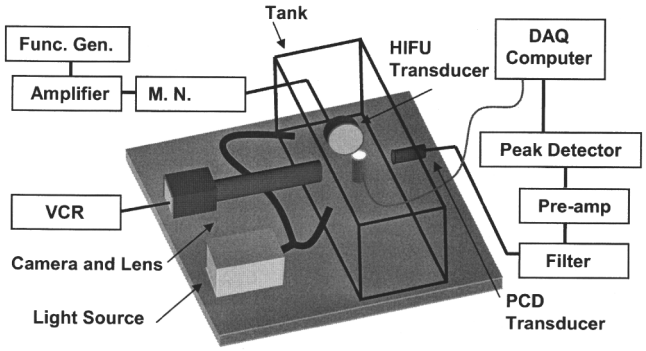

Fig. 1. Schematic showing the experimental setup used for the two studies described in the text. The HIFU source, tissue phantom (the orange cylinder in the center of the tank), lens, and camera were all mounted on individual three-axis positioning systems (not depicted). The abbreviation "M.N." stands for matching network. The two thick black lines on either side of the camera represent the goose-neck fiberoptic illuminators which are mentioned in the text. The red line connecting the tissue phantom to the DAQ computer represents the thermocouple. As discussed in the text, the thermocouple, light source, VCR, camera, and lens were only used in the VI study.

acquisition (DAQ) computer. In the VI study, the temperature near the focus of the HIFU was measured by an E-type thermocouple (Omega Engineering, 0.13-mm wire diameter). The tip of the thermocouple was positioned off axis (in a pressure null) so as to minimize any thermocouple artifacts. The DAQ computer both collected data and controlled the function generator (via GPIB) so that precise insonation times could be achieved. The lens (Navitar 18–108-mm zoom), camera (Pulnix 9701-TM), VCR (Sony DSR-11), and light source (Stocker +Yale, Lite Mite) were only used in the VI experiments.

In a general sense, the experimental protocol for each study was the same: after confocally aligning the PCD and HIFU transducers, the phantom was insonified for a set amount of time (from 7 s to in some cases 55 s) while recording the PCD signal, and (in the VI study) the thermocouple voltage as a function of time. For the CC experiments, both cw and pulsed insonation were employed; for the VI experiments, only cw insonation was used. The main difference between the two studies was the type of tissue phantom used. In the CC study, agar-graphite phantoms were used,[1,2,10] while in the VI study, optically transparent acrylamide phantoms with BSA (bovine serum albumin) were employed.[10–12]

The HIFU pressure was measured in water using a calibrated membrane hydrophone (Precision Acoustics Inc.). The corresponding focal pressure in the phantom followed from a numerical simulation of the nonlinear pressure field given the known acoustical properties of two different gel materials (1560 m/s and 0.182 Np/cm @ 1 MHz for agar-graphite phantoms; 1570 m/s and 0.02 Np/cm @ 2 MHz for acrylamide phantoms[12]) and the phantom geometry.

3. Results and discussion—VI experiments

An image of the acrylamide phantom prior to insonation is shown in Fig. 2(a). Visible in the image are the front face of the PCD transducer (the out-of-focus circle) and the tip of the thermocouple. The HIFU focal zone (defined by the half-maximum intensity contour) is indicated with a black oval. The HIFU transducer (not shown) is situated to the left of this field of view, so the HIFU beam propagates from left to right. Figure 2(b) shows the lesion that develops after a 10-s exposure (cw, 3.3 MPa, 2.0 MHz). The shape, size, and onset of this lesion are comparable to ones created in the absence of a thermocouple.

Figure 3(a) shows the temperature near the focus as a function of time for three different focal pressures. The peak PCD voltage as a function of time is shown in Fig. 3(b). The insonation time was 7 s at both 0.5 and 1.9 MPa, and 10 s at 3.3 MPa. At 0.5 MPa, there is no measurable heating, and likewise no detectable cavitation. The grouping of red data points

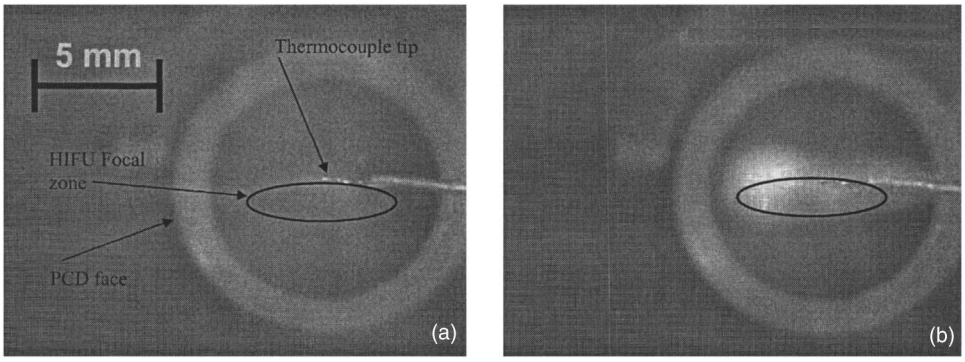

Fig. 2. Images from video, showing the focal region (a) prior to and (b) following insonation (3.3 MPa, 2.0 MHz, cw for 10 s).

around 0.4 V (the minimum nonzero output of the peak detector) is the result of increased scattering by the phantom (due to the higher insonation pressure amplitude)—it should not be interpreted as evidence of cavitation. We note that the peak-detected scattering results in a signal that is constant in time, which is markedly different than the signal when cavitation is present. The data points that fall between 0.0 and 0.4 V are attributed to an as yet undetermined source of noise and are not the result of peak-detected acoustic emissions.

The data taken at 3.3 MPa indicate that the cavitation threshold has been exceeded. Note that, for this pressure, the temperature rise is not smooth—rather, it possesses a complicated structure. From the beginning of the time series to 5 s, the temperature rises quickly and erratically, and then from 5 to 10 s the temperature decreases, despite a constant acoustic intensity from the HIFU source. Following Refs. 2 and 3, we call these two behaviors enhanced heating and bubble field shielding, respectively. Enhanced heating has been described above. Shielding can be attributed to cavitation bubbles being formed in front of the HIFU focus which shield the position of the thermocouple from acoustic energy, thus causing a decline in temperature.

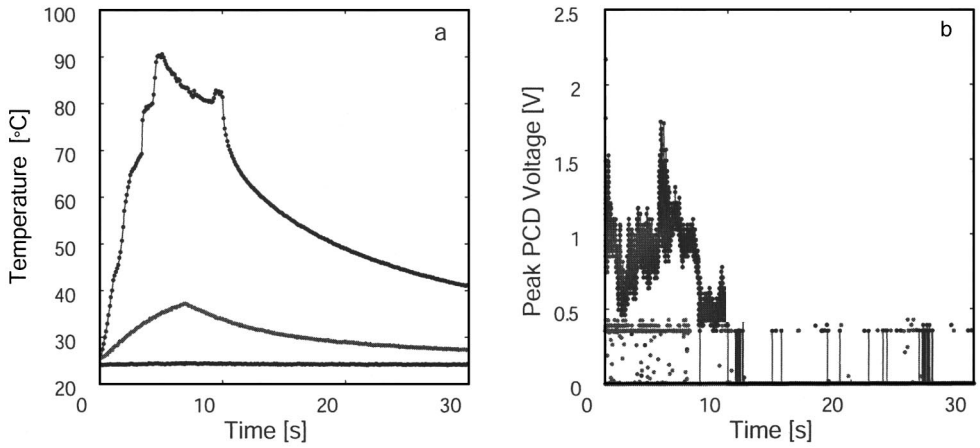

Fig. 3. Plots showing (a) temperature and (b) peak PCD signal as a function of time during and following insonation for three different focal pressures: 0.5 MPa (black), 1.9 MPa (red), and 3.3 MPa (blue). Insonation time for the two lower pressures was 7 s, and 10 s for the highest pressure, all at 2.0 MHz.

Acoustic shielding by the HIFU-induced bubble field is also reflected in the peak PCD voltage as a function of time—note the decrease in PCD voltage from 5 to 10 s. Further evidence that the HIFU energy is being shielded from the focal region is evident in the final frame of video from the highest pressure run, Fig. 2(b). A lesion was formed with dimensions roughly equivalent to that of the HIFU focus. The optically apparent lesion forms because the BSA in the acrylamide denatures (and hence loses transparency) above a certain temperature threshold.[12] Note that the lesion is thicker (in the photo's up/down direction) to the left of the thermocouple; this can be attributed to the cavitation activity that occurs prefocally—the temperature rise is greater and thus more BSA denatures. This is very similar to the *in vivo* cavitation lesions shown by Watkins *et al.*[13] The development of this lesion as a function of time can be seen in Mm. 1. The movie begins before the HIFU is turned on, and concludes after it is turned off. When the HIFU is turned on, the words "HIFU ON" appear in the lower-middle portion of the field of view. It is compelling to see that, when the thick part of the lesion begins to develop, the focal temperature begins to decrease (i.e., at roughly 5 s after the HIFU is turned on). In the movie it is clear that the lesion "grows" towards the source (which is to the left of the field of view), in agreement with other studies.[11,14]

MM 1. (in real time) showing the development of the lesion shown in Fig. 2(b). The message "HIFU ON" appears in the lower-middle portion of the field of view during insonation. Corresponding PCD and thermocouple data for the data run shown in the movie can be found in the blue line in Figs. 3(a) and (b).

4. Results and discussion—CC experiments

As a reminder, the phantoms used in the CC study were agar-graphite based, thus, there are no optical images showing the behavior of the focal zone during insonation. Furthermore, since the phantoms and instrumentation employed for this setup were different, a quantitative comparison of the PCD signals from the VI and CC experiments should not be made.

Though we defined the result of controlled cavitation to be "sustained bubble-enhanced heating," we now assume that sustained broadband emission also indicates control. We make this assumption based on results of previous experiments[1–3] which showed that enhanced heating is always accompanied by inertial cavitation. Thus, in the interest of using a noninvasive detection technique, we present PCD measurements (which we note are more likely to be used in a clinical setting) instead of thermocouple measurements. The goal of the CC experiments was to see if using pulsed insonation could change the character of the cavitation noise as a function of time—more specifically, we wanted to see if shielding could be avoided entirely. In Fig. 4 we show the results of two experimental runs, each performed at the same pressure amplitude (2.93 MPa). The red line shows the PCD signal resulting from a 20-s cw insonation. The blue line shows the PCD signal during a 5-s cw insonation followed immediately by a 60-s pulsed insonation (here the duty cycle was 20%). Note the dramatic decline in PCD signal during the cw insonation. As before, this decline can be attributed to cavitation bubbles forming in the prefocal region which shield the focal region from acoustic energy, thus inhibiting cavitation there. There is also a dramatic decline (with approximately the same negative slope as the red line) in the blue line for the first 5 s of the data run, which is not surprising since the insonation parameters for this time span were the same as for the red line. There is a drastic difference in the PCD signal after the insonation is switched from cw to pulsed. The signal first increases and then remains constant for the remainder of the experimental run. We maintain that this is evidence that pulsing the HIFU can control the cavitation activity prefocally, allowing ultrasound energy to reach the focus (i.e., it eliminates shielding).

5. Conclusions and future work

Evidence has been provided that supports the claim that enhanced heating and shielding during HIFU insonation can be attributed to cavitation activity near and in front of the focus of the HIFU transducer. In addition, we showed that some degree of control over the cavitation field can be gained by driving the sound source in a pulsed manner, rather than with cw insonation. A qualitative explanation of how the control is achieved is as follows. Assume *a priori* that there

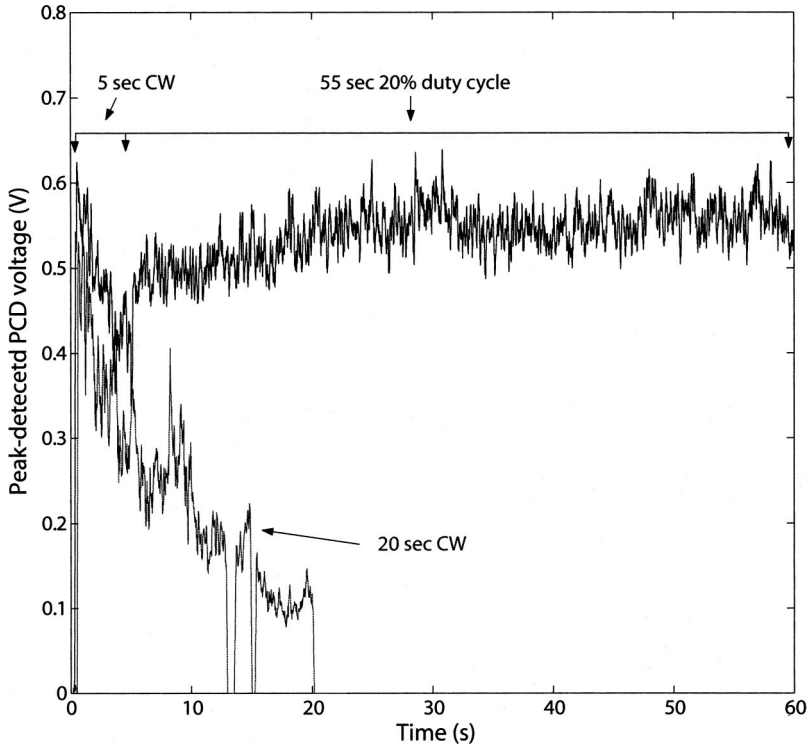

Fig. 4. Plots of the peak-detected PCD signal acquired for two different types of insonations. Red: 20 s of cw insonation; blue: 5-s of cw insonation followed by 55 s of pulsed (20% duty cycle) insonation.

are sufficient cavitation nuclei in the focus to foster the development of a cavitation field. When those nuclei are driven in a cw manner, they can grow via rectified diffusion to a size limited by the shape instability threshold (see Yang *et al.*[15] for a detailed discussion of HIFU-relevant bubble dynamics). When the bubbles become shape-unstable they break up into many smaller bubbles; these smaller bubbles subsequently grow via rectified diffusion and the growth–breakup cycle is repeated, multiplying bubble densities and physical effects (including shielding) until the HIFU is turned off.

Bubble growth during pulsed insonation is limited. Thus, fewer bubbles grow to reach the shape instability threshold and as a result fewer fragments are generated during the brief on time of the ultrasound. In fact, depending on material viscosity (see Ref. 15), bubbles undergoing short-pulse HIFU may not become shape-unstable; the bubbles grow until the end of the on time, and then dissolve (but not completely) during the off time. Since they do not dissolve completely, they make up a population of pre-existing bubbles, poised to serve as cavitation nuclei for the next on time of the ultrasound. Note that this explanation suggests the existence of an optimum duty cycle (ratio of HIFU-on time to total time) at which the HIFU source should be driven.

An obvious next step to this work is to perform cavitation control experiments with acrylamide phantoms. Doing so will allow the development of the lesion to be monitored optically. If shielding is truly absent while operating above the cavitation threshold, the shape of the lesion would coincide with the focal zone of the HIFU transducer, as opposed to the tadpole shape seen in Fig. 2(b) and Mm. 1. Furthermore, the optimal duty cycle for heating should be determined. Since the optimum duty cycle depends on the rate at which bubbles grow and

dissolve with HIFU-on and HIFU-off times, respectively, we expect it to be a function of the dissolved gas concentration and effective viscosity in the phantom.

Acknowledgments

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[9] In the paper, the first model number in the parentheses refers to equipment used in the VI experiment, and the second number refers to equipment used in the CC experiment. When only one model number appears, the same piece of equipment was used in both studies. The preamplifier used for the VI study was a Krohn-Hite 3955 filter set in by-pass mode, 40-dB total gain. In the CC study, two preamplifiers were used: an EG&G model 5185 (20 dB), and a Krohn-Hite 3950 set to 2-MHz high pass, with 40-dB total gain. In addition to the two preamplifiers, a 6-dB (50F-006) in-line attenuator was used in the CC study; thus, the total gain used in the CC study was 54 dB.
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