Monitoring HIFU Lesion Formation *In Vitro* Via The Driving Voltage

Charles R. Thomas†, Caleb H. Farny, Tianming Wu, R. Glynn Holt, and Ronald A. Roy

Department of Aerospace and Mechanical Engineering, Boston University, Boston, MA 02115
†Currently at School of Engineering, Computing and Construction Management, Roger Williams University, Bristol, RI 02809

Abstract. During insonation of tissue and tissue-mimicking materials with high-intensity focused ultrasound (HIFU), bubbles formed at or near the focus of the HIFU source have been shown to cause fluctuations in the HIFU driving voltage and current amplitudes. In this paper, we report the results of an investigation of these oscillations in an *in vitro* system – polyacrylamide phantoms with bovine serum albumin (BSA). The fluctuations in the HIFU driving voltage were interpreted to be the result of constructive and destructive interference at the transducer face caused by the incident HIFU and backscattered ultrasound from the bubbles in the lesion. Interpreting the fluctuations in this manner can lead to a determination of the location of the advancing interface of the bubbly lesion as it moves towards the HIFU transducer during CW insonation.

Keywords: HIFU, cavitation, bubbles, sensing
PACS: 47.55.Bx, 43.80.Gx, 43.80.Sh

INTRODUCTION

A challenge encountered when using HIFU to create lesions *in vivo* is monitoring the spatial extent of the developing lesion during insonation. One solution to this problem involves the detection of hyperechoic regions near or at the HIFU focus using B-mode ultrasound imaging during brief off-times of the HIFU field [1]. These hyperechoic regions have recently been shown to be due to cavitation bubbles which are formed by the HIFU and persist for some time after insonation ends [2]. Since the bubbles persist in the absence of HIFU, they act as echo contrast agents which outline the extent of the developing lesion. In this paper we describe another monitoring method which also takes advantage of the hyperechoic nature of bubbles. However it does not require a brief off time and thus is amenable to true real-time monitoring of the bubble field.

The basis for the present method is monitoring the amplitude and/or RMS value of the voltage supplied to the HIFU transducer during CW insonation. Bailey *et al.* [3] reported that rapid fluctuations in the (otherwise constant) voltage amplitude occur when bubbles form at the focus of the HIFU transducer. Here we offer an extended interpretation of these fluctuations. We have found that during the initial formation of

CP829, *Therapeutic Ultrasound: 5th International Symposium on Therapeutic Ultrasound*
edited by G. T. Clement, N. J. McDannold, and K. Hynynen

the lesion the fluctuations are due to interference at the transducer face between incident HIFU and ultrasound backscattered by bubbles (which we will call a "bubble front") which move toward the transducer during insonation. In this interpretation, the HIFU transducer acts simultaneously as a source and sensor. As the bubble front moves through a distance of one half wavelength, the interference at the HIFU transducer will go through one cycle of constructive to destructive interference. Thus by tracking the cyclic variation of the HIFU drive voltage (RMS or amplitude) versus elapsed time, information about the time-dependent spatial extent (in the direction from the focus to the transducer) of the bubble front can be determined.

EXPERIMENTAL METHODS

The advantage of the *in vitro* experiments (transparent polyacrylamide phantoms with BSA [4] were used) described in this paper was the ability to simultaneously monitor the HIFU driving voltage and optically image the spatial development of the lesion as demarcated by denatured BSA. In addition, the bubble activity was also monitored by a focused passive cavitation detector (PCD) aligned confocally with the HIFU transducer.

The set up is the same as in [5], with the addition of an RMS-to-DC converter chip (Analog Devices, AD637) for measuring the true RMS voltage across the HIFU transducer in real time (integration time ~25 ms). This analog RMS signal was both digitized and fed to the left audio channel of a VCR which was used to store video taken during experimental runs. In this paper we report voltage amplitudes which were calculated from the measurements of RMS voltage using a calibration curve measured *in situ*. To be clear, the lighting here was also the same as in [5] – the illuminator was behind the camera pointing towards the location of the HIFU focus.

In the experimental run discussed in this paper we employed a focal pressure of 12.3 MPa, a frequency of 2 MHz, and cw insonations lasting 5 seconds each. The focal pressure was determined by measuring the transducer voltage and using a calibrated measurement of the focal pressure in water and a nonlinear numerical simulation to account for scattering and absorption in the phantom material.

RESULTS AND DISCUSSION

A series of images captured by the camera during an experimental run in which bubbles were present is shown in Fig. 1. The times in the upper right-hand corner of the individual frames refer to time elapsed since HIFU was turned on. The thick white circle in each frame is the outer rim of the PCD transducer as viewed from the front. The bright spot at the center of the circle at time 0.00 s is due to a reflection – not a bubble. The first pressure null of the HIFU field (the black ellipse), the forward interface of the tissue phantom (the white line), a spatial scale and the face of the PCD transducer are indicated in the frame corresponding to time 0 s. The HIFU transducer was located to the left of the field of view.

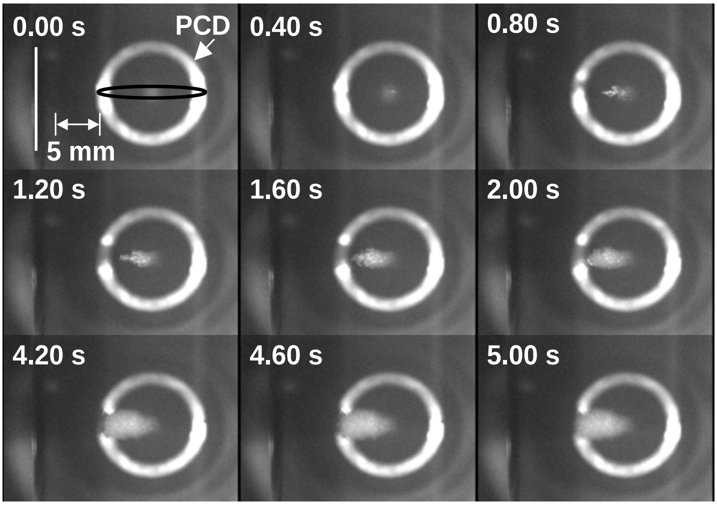

FIGURE 1. Frames taken from video of one experimental run. Note that the bubble front takes some time (~0.40s) to form, and that its leftward progress slows dramatically after roughly 2 seconds. The HIFU transducer (not shown) generates a beam that projects from left to right.

The images span the entire duration of HIFU exposure. The bubble front first appeared on the images as a bright spot approximately 0.40 s after the HIFU was turned on. During exposure, the bubble front moved towards the HIFU transducer, in agreement with other studies [3,5,6], leaving denatured BSA in its wake. The position of the left-most extent of the bubble front was determined using an image processing software package (EPIX, X-cap), and it is plotted relative to the focal position of the HIFU transducer as a function of time in Fig. 2. Note that the advance of the bubble front stops after about 2 seconds of HIFU insonation.

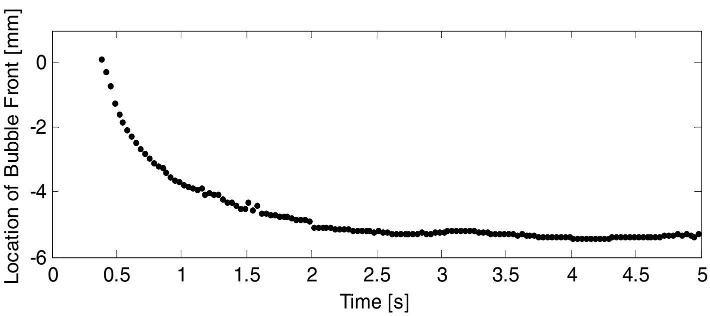

FIGURE 2. Video measurements of the left-most edge of the lesion. The data are plotted relative to the focal plane of the HIFU transducer, with negative quantities corresponding to pre-focal positions.

Figure 3 contains plots of the peak PCD voltage (an indicator of inertial cavitation activity), and the amplitude of the HIFU drive voltage corresponding to the images in Fig. 1. The peak in the PCD signal (Fig. 3a) is caused by a combination of the moving bubble field and the finite dimensions of the PCD sensing region (order 650 μm in diameter). In this data run, the cavitation field initially developed within the sensing zone of the PCD. The resulting broad-band noise signal reached a maximum level at the zenith of inertial cavitation activity and declined as the bubble front moved out of the sensing zone and towards the HIFU transducer.

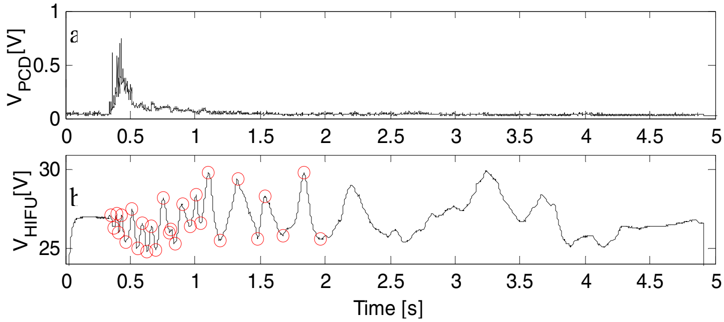

FIGURE 3. Plots of the PCD signal (a) and HIFU voltage amplitude (b). The peak in the PCD signal corresponds to the formation, growth, and eventual departure of the bubble field from the PCD sensing region. The circles in (b) denote extrema in the HIFU voltage amplitude.

In Fig. 3a notice that the fluctuations in the HIFU driving signal begin after a delay of about 0.4 seconds. This mirrors the fact that the bubble front took some time to form (see Fig. 1). The data plotted in Fig. 3b is typical – a period of fast, fairly regular oscillations (in this case, from time 0 up to about 2 seconds), followed by oscillations which have much more irregular periods. The times of the extrema of the HIFU voltage amplitude (circled in Fig. 3b), were obtained and used to determine the left most extent of the bubble front. To do this, we assume that the location of the bubble front at the onset of HIFU drive oscillations (0.4 s) is in the focal plane of the HIFU transducer and every subsequent cycle of HIFU drive oscillation corresponds to the displacement of the bubble front by one half of an acoustic wavelength (≈0.8 mm for a 2 MHz field in the acrylamide phantom).

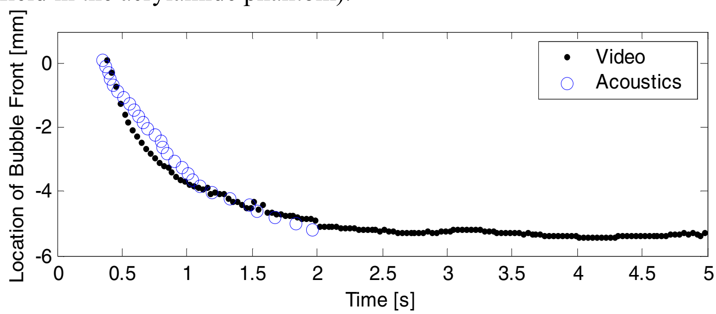

FIGURE 4. Comparison of the two different methods described in the text for determining the proximal boundary of the advancing cavitation zone.

We now have two means for monitoring in real time the position of the advancing cavitation zone (and, by extension, the bubbly HIFU lesion). One is optical and only applicable to transparent phantom studies. The other is acoustical and could be employed in systems without optical access, including *in vivo*. The former serves as a gold standard for assessing the accuracy of the latter; the direct comparison is plotted in Fig. 4. For roughly two seconds, the results of the two methods agree well. After two seconds, the periodic oscillations are absent (see Fig. 3b) and the acoustical method is neither applicable nor useful, for by now the advance of the bubbly lesion has halted.

SUMMARY AND CONCLUSION

Polyacrylamide phantoms with BSA were used to visualize the development of the bubble front which often accompanies thermal lesions in an *in vitro* model. By synchronizing video imagery of the evolving bubbly lesion with measurements of the HIFU RMS drive voltage, we conclude that the oscillations observed in the HIFU drive are caused by interference of the incident HIFU and backscattered ultrasound from the advancing bubble front. We stress here that the bubble front must be moving in order to produce the oscillations. As the bubble front progresses, the phase of the backscattered pressure field at the transducer face (where the interference takes place) varies periodically. The resulting interference effect between incident and scattered sound also varies periodically as the front advances and is manifested as a periodic fluctuation in the HIFU drive voltage amplitude versus elapsed exposure time. Since the backscattered sound traverses twice the distance from the transducer to the bubble front, every complete oscillation in the HIFU drive implies that the bubble front has advanced one half wavelength. Thus, assuming that the bubble front also defines the size of the lesion, simply by counting cycles in the HIFU voltage amplitude, potentially valuable information concerning the spatial extent of the lesion can be determined.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the financial support of the Department of the Army (award number DAMD17-02-2-0014) and The Center for Subsurface Sensing and Imaging Systems, under the Engineering Research Centers Program of the National Science Foundation (award number EEC-9986821).

REFERENCES

1. Vaezy, S., Shi, X., Martin, R.W., Chi, E., Nelson, P.I., Bailey, M.R., Crum, L.A., Ultrasound in Medicine and Biology. **27**(1): 33-41, 2001.
2. Rabkin, B.A., Zderic, V., and Vaezy, S., Ultrasound in Medicine and Biology. **31**(7): 947-956, 2005.
3. Bailey, M.R., Reed, J., Anand, A., Kaczkowski, P., Kreider, W., Vaezy, S., Crum, L.A., Seip, R., Tavakkoli, J., and Sanghvi, N.T., in Proceedings of the 3rd International Symposium on Therapeutic Ultrasound, 43-48, 2003.
4. Lafon, C., Kaczkowski, P.J., Vaezy, S., Noble, M., and Sapoznikov, O.A., IEEE Ultrasonics Symposium, 1295-1298, 2001.
5. Thomas, C., Farny, C.H., Coussios, C., Roy, R.A. and Holt, R.G., Acoustic Research Letters Online, **6**(3): 182-187, 2005.
6. Chen, W.S., Lafon, C., Matula, T.J., Vaezy, S. and Crum, L.A., Acoutics Research Letters Online **4**: 41-46, 2003.