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● *Original Contribution*

HYPERECHO IN ULTRASOUND IMAGES OF HIFU THERAPY: INVOLVEMENT OF CAVITATION

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Abstract—High-intensity focused ultrasound (US), or HIFU, treatment of soft tissues has been shown to result in a hyperechoic region in B-mode US images. We report on detecting cavitation *in vivo* in correlation with the appearance of a hyperechoic region. The US system consisted of a HIFU transducer (3.3 MHz), a broadband A-mode transducer for active and passive cavitation detection and an US-imaging probe that were all confocal and synchronized. HIFU, at *in situ* intensities of 220 to 1710 W/cm^2, was applied for 10 s to pig muscles *in vivo*. Active and passive cavitation detection results showed a strong correlation between the onset of cavitation and the appearance of a hyperechoic region. Passive cavitation detection results showed that inertial cavitation typically occurred prior (within 0.5 s) to the appearance of a hyperechoic region. The observed cavitation activity confirms that bubbles are present during the formation of a hyperechoic region at the HIFU focus. (E-mail: vaezy@u.washington.edu) © 2005 World Federation for Ultrasound in Medicine & Biology.

Key Words: **High-intensity focused ultrasound (HIFU), Cavitation, Ultrasound visualization, *In vivo*, Bubbles, Therapy guidance, Monitoring.**

INTRODUCTION

High-intensity focused ultrasound (US), or HIFU, has been explored for its therapeutic use in the treatment of tumors (Gianfelice et al. 2003; Hynynen et al. 2001; Rowland et al. 1997; Van Leenders et al. 2000; Wu et al. 2002, 2003), hemostasis (Delon-Martin et al. 1995; Hynynen et al. 1996; Martin et al. 1999; Vaezy et al. 2001a) and the transfection of DNA (Miller and Song 2003). The main advantage of HIFU is its noninvasive nature; the focus where therapy occurs can be placed deep within a patient's body without affecting the intervening tissue layers. To use this advantage, the development of a real-time targeting and monitoring method for the initial placement of the focus at the appropriate therapy site and the observation of changes to tissue during treatment is required.

Current methods of guiding and monitoring transcutaneous applications of HIFU for noninvasive therapies include magnetic resonance imaging and diagnostic US imaging techniques. Although magnetic resonance imaging provides excellent soft tissue contrast and the ability to measure temperatures at the HIFU treatment site, it has several drawbacks, including its overall expense, nonportability, the need to use special HIFU equipment that does not interfere with the magnetic field and the slow rate of image presentation (reported as 5 to 10 s after HIFU exposure) (Bohris et al. 2001; Righetti et al. 1999). US guidance of HIFU therapy has been used because of the portability, low cost, real-time image processing, simple integration with HIFU instruments and extensive availability of diagnostic US (Vaezy et al. 2001b; Wu et al. 2003). The use of US visualization for the guidance and monitoring of HIFU therapies most often relies on the appearance of a hyperechoic region in the US image (Fry et al. 1995; ter Haar et al. 1989; Wu et al. 2003).

It has been postulated that the formation of a hyperechoic region at the HIFU treatment site results from bubble activity generated during HIFU exposure (Bailey et al. 2001; ter Haar et al. 1989; Vaezy et al. 2001b; Wu et al. 2003). A growing body of evidence suggests the presence of microbubbles at the focal site. First, coagulative necrosis lesions could not be produced beyond the hyperechoic region, interpreted as resulting from the inability of US to pass through microbubbles (Fry et al.

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1995). Second, bright speckle-size spots (assumed to be bubbles) were observed, with real-time US monitoring, escaping into the vascular system of the liver from the focal site during *in vivo* HIFU exposure (Vaezy et al. 2001b). Third, production of hyperechoic bright spots in the HIFU near field (between the HIFU focus and transducer) was observed only in tissues that shared the same vascular network with the tissue where the original hyperechoic region was present. It was, therefore, concluded that bubbles were produced at the focus during the formation of the initial hyperechoic region and perfused to adjacent tissues in the near field, resulting in the production of an additional hyperechoic region (Fry et al. 1995). Fourth, backscattering of US has been shown not to change in a significant manner due to thermal coagulation of tissue alone (*i.e.*, in the absence of bubbles) (Bush et al. 1993). During the studies described above, no measurements of acoustic emissions distinct to cavitation were performed.

During HIFU ablation of dog thigh muscle *in vivo*, Hynynen (1991) observed that the hyperechoic region appeared after the first HIFU pulse in which inertial cavitation was detected. In a study to determine if cavitation occurred at the focal site of a lithotripter *in vivo*, Coleman et al. (1996), using a 1-MHz hydrophone, found that the acoustic emission, as distinct from cavitation, at the shock-wave focus correlated with the appearance of a hyperechoic region in the US images immediately posttreatment. As a result of this study, the presence of a hyperechoic region in an US image has been used to determine if cavitation occurred during lithotripsy (Tavakkoli et al. 1997).

The presence of cavitation in the US field has also been shown to correlate with a rapid rise in temperature *in vitro* (Holt and Roy 2001) and *in vivo* (Hynynen 1991; Sokka et al. 2003), as well as with the unpredictable shape of the HIFU lesion *in vitro* (Bailey et al. 2001) and *in vivo* (Clarke and ter Haar 1997; Hynynen 1991). Because unpredictable lesion formation and a rapid rise in temperature may result from the presence of bubbles in the US field, avoidance of cavitation was proposed for better control of lesion formation during HIFU treatment (Holt and Roy 2001; Hynynen 1991). Short HIFU bursts ($<$1 s) at the minimum intensity threshold for producing a hyperechoic region have been shown to produce no tissue damage *in vivo* (Vaezy et al. 2001b). Therefore, it may be possible to use nonlethal short HIFU bursts for targeting the treatment site under US guidance.

It is important to determine the role of cavitation in the visualization of a hyperechoic region. This is necessary from both the perspective of determining the location of the HIFU focus before commencement of treatment and for monitoring HIFU therapies to avoid achieving tissue temperatures above the therapeutic range, resulting in an unpredictable and more extensive lesion than desired. Our objective was to determine, by active and passive cavitation detection, if cavitation was present during the visualization of HIFU treatment as a bright hyperechoic region on conventional B-mode US imaging.

MATERIALS AND METHODS

Animal model

A total of 6 juvenile pigs weighing 25 to 35 kg each were used. The experimental protocol was approved by the Animal Care Committee at the University of Washington and conducted according to the guidelines of the United States National Institutes of Health (NIH) for use of laboratory animals. Initial sedation of the pigs was done with an IM injection of a mixture containing acepromazine (1 mg/kg) and ketamine (22 mg/kg). After transportation to the experimental room, a dose of 3.5 to 4 mL of ketamine/xylazine (1:8 ratio) was used to anesthetize each animal. A tracheal tube was then introduced for maintenance of anesthesia (isofluorane 1 to 3%) during the experiment.

HIFU exposures were performed in the muscles located adjacent to the spine (longissimus thoracis) and in the outer thigh of the pig hind limb (biceps femoris and rectus femoris). These sites were chosen because they offer a large thick region (4 to 6 cm) of muscle for HIFU exposures. To maintain a smooth layer on the muscle surface for coupling the HIFU transducer water cone, the muscle surface was exposed with a scalpel. This reduced the occurrence of bubbles trapped at the HIFU tissue interface. In addition, the US path was made consistent by removing the skin and underlying fat that are variable in depth along the muscle. HIFU exposures were done at 2-cm intervals along the muscles. After the experiments, the animals were euthanized with an overdose of the anesthetic mixture, followed by 20 mL KCl saturated saline.

HIFU, US imaging and cavitation detection system

A single-element 1.1-MHz concave air-backed HIFU transducer (focal depth of 6.3 cm and f-number of 0.9; Sonic Concepts, Woodinville, WA, USA) was driven at the frequency of its third harmonic (3.32 MHz). The focus had a full-width half-maximum beam width and length of 0.45 mm and 4 mm, respectively, measured using a calibrated polyvinylidene difluoride needle hydrophone (NTR Systems, Seattle, WA, USA). A radiation force balance technique was used to determine the acoustic power output (Christensen 1988). In all experiments, the duty cycle of HIFU was 80% at a pulse repetition frequency of 6.26 Hz. The transducer was manufactured with a 2 cm-wide hole at its center for