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● *Original Contribution*

INTERACTIONS BETWEEN CONSECUTIVE SONICATIONS FOR CHARACTERIZING THE THERMAL MECHANISM IN FOCUSED ULTRASOUND THERAPY

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Abstract—The use of focused ultrasound for thermal ablation or therapy has become a promising modality due to its high selectivity and noninvasiveness. The temperature increase that induces thermal necrosis in the focal beam area has been reported to be attributed to the absorption of ultrasound energy and heating enhancement by acoustic cavitation. The purpose of this study is to propose a novel experimental arrangement to observe the thermal lesion formation and to demonstrate that the presence of the ultrasound-induced, macroscopically-visible bubbles may exert a key effect in thermal lesion formation. In our experiments, consecutive sonications with orthogonal intersections were applied to observe the thermal lesion interaction induced by 577- or 1155-kHz ultrasound. Results showed that the 1155-kHz heating was dominated by ultrasound energy absorption, with blocking of consecutive sonications being evident only rarely. However, in 577-kHz sonications, the thermal process was dominated by inertial cavitation and the corresponding ultrasound-induced, macroscopically-visible bubbles, which was verified from the later lesion being blocked by the former one and direct observation from light microscopy. This study demonstrates that the operating frequency for ultrasound thermal ablation should be selected based on the intended specific thermal mechanisms to be induced. (E-mail: winli@ntu.edu.tw) © 2006 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Focused ultrasound, Thermal therapy, Inertial cavitation, Ultrasound- induced macroscopically-visible bubbles.**

INTRODUCTION

The use of high-intensity focused ultrasound for noninvasive tissue thermal ablation has increased in popularity over the past decades (Chapelon et al. 1991; Dunn and Fry 1971; Fry and Fry 1953; Hynynen et al. 1993; Sanghvi and Hawes 1994; ter Haar 1995; Vaezy et al. 1998). Focused ultrasound in the therapeutic frequency range (0.5 to 3.5 MHz) offers good tissue penetration and can result in highly focused energy deposition (Nyborg 1981; Nyborg 2001). Absorption of the focused energy by tissues for only a few seconds can induce localized large temperature elevations (30 to 55°C) and generate irreversible tissue necrosis at the target region, while surrounding tissue remains undamaged.

Successful treatment relies on the temperature increase at the focal region. The absorption of ultrasound energy whilst it is attenuated during transmission in mammalian tissues serves as a direct ablation mechanism. The resulting temperature elevation can be predicted by the bioheat transfer equation that considers tissue absorption (nearly proportional to the operating frequency [Duck 1990]), conduction and convection (Pennes 1948; Mahoney et al. 2001). Advanced models that consider nonlinear effects during sonications were also attempted to explain the process and mechanism of thermal lesion formation (Chavrier et al. 2000; Connor and Hynynen 2002; Meaney et al. 2000; Watkin et al. 1996).

In addition to the absorption of acoustic energy, acoustic cavitation also plays an important role in the

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temperature increase induced by ultrasound. The acoustic cavitation is defined as "the formation of one or more pockets of gas in a liquid, where formation refers, in a general sense, both to the creation of a new cavity or the expansion of a preexisting one to a size where macroscopic effects can be observed" (Apfel 1981). Within the acoustic cavitation process, the transient acoustic cavitation (also known as the inertial cavitation) may occur, which usually refers to the process in which bubbles, under the excitation of ultrasonic energy, collapse violently, resulting in strong ultrasonic energy emissions as well as large and rapid local temperature increases. The temperature within a collapsing gas body can reach 10000°K (Flynn 1964), based on theoretical estimation, which has been verified experimentally (Flannigan and Suslick 2005). Hynynen et al. (1991) have reported that the occurrence of inertial cavitation in *in vivo* muscle tissue can significantly enhance the heating produced by focused ultrasound. Furthermore, the inertial cavitation has been found to be frequency-dependent in many previous studies, which concluded that the required intensity to produce inertial cavitation would be higher in high-frequency ultrasound exposure than low-frequency ultrasound exposure (Flynn 1964; Hynynen 1991).

In addition to the transient cavitation effect, there are numerous studies that point out that macroscopically-visible bubbles and their accompanying effects can be produced during the sonication process. Previous research shows that acoustic bubbles were detected in the hind limbs of guinea pigs during continuous ultrasound exposure, with bubble size ranging from 5 μm to over 100 μm (ter Haar and Daniels 1981; ter Haar et al. 1982). Later on, Daniels et al. (1987) successfully demonstrated that macroscopically-visible gas bubbles, which are better for real-time observation and quantitative analysis, could be produced in an agar-based gel by either pulsed or continuous ultrasound exposure. Large bubbles have also been observed in cross-sections of endothelial cells in venule and capillary *in vivo*, beef, mouse liver and mouse uterus (Hug and Pape 1954; Kobayashi et al. 2002; ter Haar and Daniels 1981; ter Haar et al. 1982). Since the size of macroscopically-visible bubbles is close to the ultrasound wavelength, ultrasound scattering occurring through a cavity-rich beam path may significantly alter the lesion formation. The macroscopically-visible bubbles in the above investigation were all induced by planar transducers under the pulsed mode sonication. The alternation effect of focused ultrasound on induced thermal lesions has not been thoroughly investigated. Due to the fact that the contributions of ultrasound energy absorption and acoustic cavitation to the thermal ablation process are both frequency-dependent, it is important to understand which mechanism will be the major contributor at a selected operating frequency. The purpose of this study was to elucidate the mechanism underlying the transition from ultrasonic energy absorption to propagating wave interference caused by sonication-induced cavities as a function of the driving frequency in focused ultrasound thermal therapy.

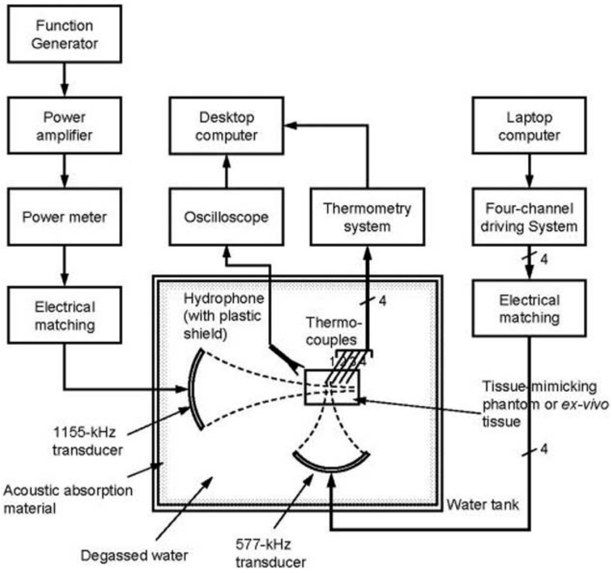

Fig. 1. System set-up for performing measurements in transparent phantoms and *ex vivo* tissues.

The thermal lesions induced by low- and high-frequency ultrasound (577 and 1155 kHz, respectively) were observed. The proposed approach attempted to answer the following *a priori* hypotheses: (1) whether the ultrasound frequency plays a key role in determining the thermal mechanism of lesion formation, (2) whether macroscopically-visible bubbles can be produced by low-frequency focused ultrasound exposure and (3) if this is the case, whether it influences the focal beam propagation as well as the resulting lesion shape.

MATERIALS AND METHODS

System set-up and experimental procedure

Figure 1 shows a block diagram of the experimental set-up used to observe the lesion's development. Orthogonally intersecting focused ultrasound beams were set up to observe the interactions between created lesions. The sonication was provided by two spherically concave PZT-4 ultrasound transducers with operating frequencies of 577 and 1155 kHz (components from Elecerom, Taoyuan, Taiwan, and assembled in-house; both had a diameter of 10 cm and their radii of curvature were 10 and 20 cm, respectively).

The 577- and 1155-kHz ultrasound transducers were electrically excited separately to characterize suitable sonication parameters to induce thermal lesions in