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Thermal Effects Induced in Liver Tissues by Pulsed Focused Ultrasonic Beams from Annular Array Transducer

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Many therapeutic applications of pulsed focused ultrasound are based on heating of detected lesions which may be localized in tissues at different depths under the skin. In order to concentrate the acoustic energy inside tissues at desired depths a new approach using a planar multi-element annular array transducer with an electronically adjusted time-delay of excitation of its elements, was proposed. The 7-elements annular array transducer with 2.4 MHz center operating frequency and 20 mm outer diameter was produced. All its elements (central disc and 6 rings) had the same radiating area. The main purpose of this study was to investigate thermal fields induced in bovine liver *in vitro* by pulsed focused ultrasonic beams with various acoustic properties and electronically steered focal plane generated from the annular array transducer used. The measurements were performed for the radiating beams with the 20 mm focal depth. In order to maximize nonlinear effects introducing the important local temperature rise, the measurements have been performed in two-layer media comprising of a water layer, whose thickness was specific for the transducer used and equal to 13 mm, and the second layer of a bovine liver with a thickness of 20 mm. The thickness of the water layer was determined numerically as the axial distance where the amplitude of the second harmonics started to increase rapidly. The measurements of the temperature rise *versus* time were performed using a thermocouple placed inside the liver at the focus of the beam. The temperature rise induced in the bovine liver *in vitro* by beams with the average acoustic power of 1 W, 2 W and 3 W and duty cycle of 1/5, 1/15 and 1/30, respectively, have been measured. For each beam used the exposure time needed for the local tissue heating to the temperature of 43°C (used in therapies based on ultrasonic enhancement of drug delivery or in therapies involving stimulation of immune system by enhancement of the heat shock proteins expression) and to the temperature of 56°C (used in HIFU therapies) was determined. Two sets of measurements were done for each beam considered. First, the thermocouple measurement of the temperature rise was done and next, the real-time monitoring of dynamics of growth of the necrosis area by using ultrasonic imaging technique, while the sample was exposed to the same acoustic beam. It was found that the necrosis area becomes visible in the ultrasonic image only for beams with the average acoustic power of 3 W, although after cutting the sample the thermo ablated area was visible with the naked eye even for the beams with lower acoustic power. The quantitative analysis of the obtained results allowed to determine the exposure time needed to get the necrosis area visible in the ultrasonic image.

Keywords: annular array transducer, pulsed focused nonlinear ultrasound, electronically moved focus, tissue heating, biological effects, tissue necrosis.

1. Introduction

In recent years, the number of therapeutic applications of pulsed focused ultrasonic beams with various intensities is steadily increasing (ter Haar, 2007). All these applications need a knowledge of both the temporal and spatial distributions of acoustic pressure and temperature in the beams in order to plan an effective treatment with minimal level of adverse side effects. Many therapeutic applications of pulsed focused ultrasound are based on heating of detected lesions which may be localized in tissues at different depths under the skin. In order to raise the temperature of the tumor, a focal spot of an ultrasonic beam should be positioned directly at the lesion site. The focusing of acoustic energy in tissue at a desired depth can be achieved using single-element circular concave transducers with selected diameters and radii of curvature. This solution is however inefficient because it requires using a set of transducers with different focal depth depending on the depth of the tumor under treatment. In order to solve this problem a new approach, allowing to concentrate the acoustic energy inside tissues at desired depths using a planar multi-element annular array transducer with an electronically adjusted time-delay of excitation of its elements, was proposed. For the applications based on thermo ablation of detected lesions localized inside tissues at different depths the tumor temperature should be raised above 56°C (HIFU techniques). Some treatments using pulsed focused ultrasound requires the beams with lower intensity to heat tissues up to 43°C (techniques based on enhancement of drug uptake or on stimulation of an immune system) (ter Haar, 2007; Zhang *et al.*, 2008). The range of biological effects induced in tumors by pulsed focused ultrasound depends on beams acoustic properties determined by the initial tone bursts frequency, intensity, duration and duty-cycle as well as exposure time. As already noted, the main purpose of this work was to investigate the thermal fields induced in bovine liver *in vitro* by the pulsed focused ultrasound beams with a 20 mm focal length and various acoustic properties generated from the planar 7-elements annular array transducer whose elements have the same area of a radiating surface. The selection of the animal organ was done in order to demonstrate the possibilities of using the annular array transducer for treatment of a hepatocellular carcinoma (HCC).

This paper is organized in the following way: in the next section the experimental setup and methodology of measurements of the temperature rises induced in a fresh bovine liver *in vitro* by pulsed focused ultrasound beams with various acoustic properties is described. Then, detailed description of the experimental setup for ultrasonic imaging of the necrosis area induced inside the liver due to acoustic energy is given. Finally, the measurement results are summarized along with the conclusions indicating that for the beams with the average acoustic power less than 3 W the necrosis area induced in the bovine liver *in vitro* was not visible in the ultrasonic image although it was visible with the naked eye after cutting the sample.

2. Materials and methods

All measurements were carried out at 35°C in the measurement setup shown in Fig. 1.

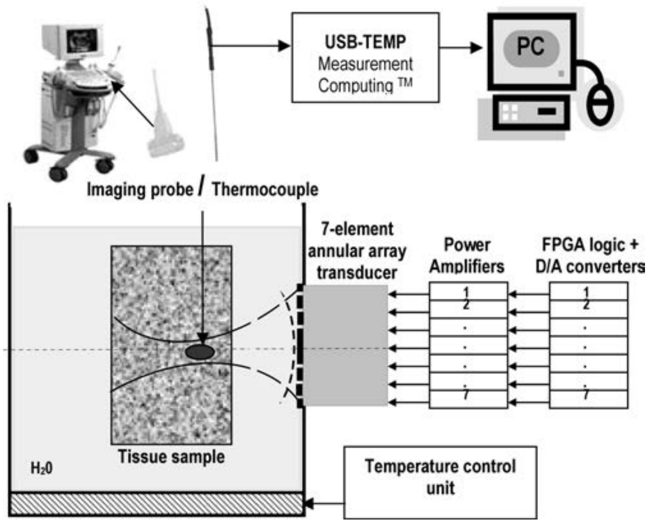

Fig. 1. Experimental setup.

The acoustic pressure tone bursts were generated using 7-element annular array transducer with an outer diameter of $2a_{\mathrm{eff}} = 20$ mm and centre frequency of 2.4 MHz. The transducer was fabricated out of Pz26 ceramics (Ferroperm, Kvistgart, Denmark). All elements of the transducer had the same area to provide a uniform pressure distribution at the surface. The detailed description of the transducer design was published previously (Secomski *et al.*, 2010). The transducer was air-backed and had a quarter-wave matching layer. The transmission electronics were based on seven custom made broadband power amplifiers controlled by seven D/A converters AD9717 and programmable logic system FPGA

(Altera Aria EP1AGX). The transducer's elements were driven by tone bursts with various amplitude, duration, duty-cycle and time-delay to produce pulsed focused ultrasonic fields with the focal spot at the desired distance. Time-delays of pulses exciting the individual elements were calculated using the Matcad™ software and processed to the digital files using the software package Altera Quartus. For the measurements performed in this work the time-delays of the tone bursts have been programmed to get the focused beams with the focal length of 20 mm. The voltage applied to the elements was varied to produce the beams with the average acoustic power of 1 W, 2 W and 3 W. The acoustic power was measured using the Power Balance UPM-DT-1E (Ohmic Instruments, Easton, USA).

The annular array transducer was mounted in a water tank with controlled temperature. The source pressures were determined using two techniques: first – by the power balance and second – by the calibrated hydrophones. The measurements of the source pressure were carried out in water. The pressure amplitudes of the initial tone bursts and the radiating aperture apodization function at the transducer surface were determined using the comparison-fitting method for both the axial and radial pressure variations measured and calculated in water. For calculations the nonlinear propagation model based on the TAWE approach (Wójcik *et al.*, 2006) allowing the numerical solution of the second order nonlinear differential wave equation for axially symmetric sources was used. The radial pressure variations were measured at a distance of 5 mm from the transducer surface by the 0.2 mm needle hydrophone S/N 1661 (Precision Acoustics, Dorchester, UK). The axial harmonic pressure distributions in the nonlinear beams were measured at the axial range from 1 cm to 8 cm using the calibrated broadband bilaminar PVDF membrane hydrophone (Unisyn, formerly Sonora Medical Systems Inc. SN S5-153, Longmont, CO, USA) with an integrated preamplifier. The measured axial and radial pressure distributions were compared with those simulated numerically and by iteration process the source pressures were found to be of P_0 = 219 kPa, 309 kPa and 379 kPa and the apodization function of $P_0(r) = P_0|1 - (r/a_{\text{eff}})^{10}|$. For the duty-cycle of 0.2 these values corresponded to the beams with the average acoustic power of 1 W, 2 W and 3 W, respectively. The agreement between two methods was within 10%.

All tissue samples being investigated were fresh because the bovine liver was provided within 4 hours after slaughter. Each liver sample was degassed, inserted in a cylindrical chamber with an acoustically transparent 20-μm thick Mylar film stretched over each end and next immersed in the water tank. The chamber with an internal diameter of 30 mm and height of 20 mm was used. The distance between the transducer surface and the water/liver interface was determined theoretically using the nonlinear propagation model. This distance was selected as the axial distance at which the 2nd harmonics amplitude – for the tone bursts generated from the transducer used and nonlinearly distorted during propagation in water – started to grow rapidly. As has been shown in previous publications (Kujawska *et al.*, 2009; Kujawska *et al.*, 2011) this distance is specific for each transducer with $ka \gg 1$ and does not depend on the pressure amplitude on the source producing weak to moderate nonlinear fields in water. The choice of this distance was done to maximize the harmonics generation effect being one of the reasons of the temperature rise induced in tissues by nonlinear ultrasound. The conditions of weak to moderate nonlinear fields were determined in (Baker *et al.*, 1988; Nachef *et al.*, 1995) showing that the ratio of the discontinuity distance to the Rayleigh distance for these fields should be larger than 0.3. Three source-pressure levels used in this work fulfill this requirement. For the transducer used the distance at which the 2nd harmonics amplitude started to grow rapidly for tone bursts propagating in water was determined to be 13 mm. For measurements of temperature rises induced in bovine liver samples during their exposure to focused ultrasound the thermocouple TP-201 (Czaki, Warsaw, Poland) with a diameter of 0.2 mm was used. It was inserted inside the bovine liver sample in the beam focus using the thin 0.5 mm diameter syringe needle. The uncertainty of position of the thermocouple tip was about $\pm$ 0.5 mm. Due to small diameter of the thermocouple its influence on measurement results was negligible. The temperature rise detected by thermocouple was recorded with a 1 second step by the USB-TEMP unit (Measurement Computing, Norton, USA) and transferred to the PC memory. For processing of the data obtained and visualizing the temperature rise *versus* time curves the software TracerDAQ was used.

For imaging the biological effects induced locally inside bovine liver samples by focused ultrasound beams with various acoustic properties the ultrasonic imaging system Antares (Siemens Acuson, Mountain View, USA) equipped with the linear array probe VF 13-5 operating at the 10 MHz frequency was used. Monitoring of dynamics of changes in the ultrasonic image was done in real-time.

3. Results and discussion

The measurements of the temperature rises induced in the bovine liver *in vitro* by the pulsed focused ultrasound beams with the average acoustic power of 1 W, 2 W and 3 W and a duty-cycle varied from 1/30 to 1/5 have been carried out. The beams were generated from the 7-elements planar annular array transducer in two-layer media comprising of a 13 mm water layer and a 20 mm layer of bovine liver. The thickness of the water layer was determined using nonlinear propagation model as a distance at which the 2nd harmonics amplitude for the tone bursts propagating in water started to grow rapidly. The beams were focused at a 20 mm distance from the transducer face by electronic steering of the time-delay of pulses driving the transducer elements. Their focal plane was located inside the bovine liver sample. The measurement results are presented in Fig. 2 and Fig. 3. In Fig. 2 the temperature rises induced in the focus of the pulsed nonlinear beams with the average acoustic power of 1 W, 2 W and 3 W and duty-cycle of 0.2 (20 cycles/100 cycles) are shown. Plots in Fig. 2 indicate that

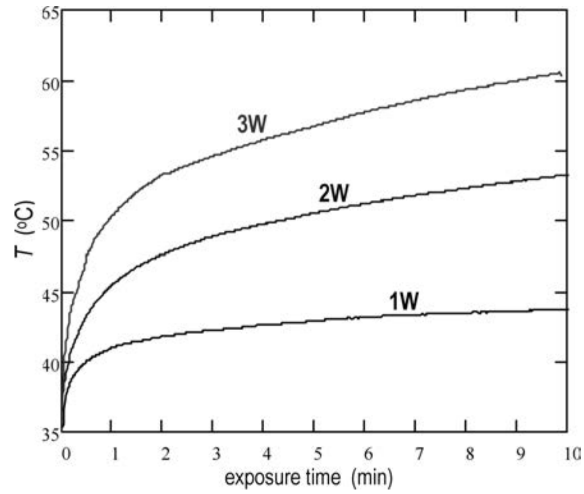

Fig. 2. Temperature rise locally induced in bovine liver *in vitro* by pulsed focused ultrasonic beams with a duty-cycle of 0.2 and the average acoustic power varied between 1 W and 3 W and measured during 10 min exposure in the beam focus.

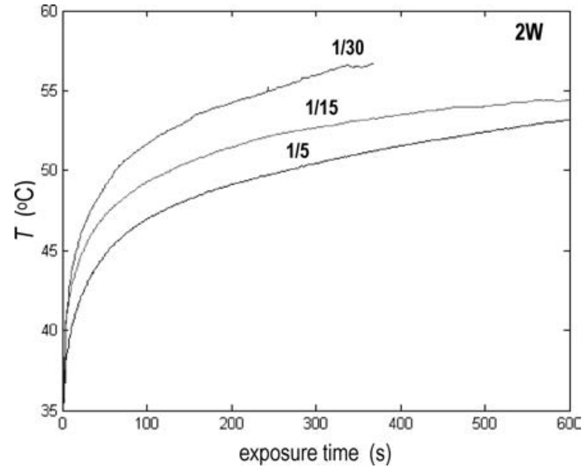

Fig. 3. Temperature rise induced in bovine liver *in vitro* by pulsed focused ultrasound beams with an acoustic power of 2 W and varied duty-cycle measured during 10 min exposure time. Duty-cycle was varied from 1/30 (5 cycles/150 cycles) *via* 1/15 (10c/150c) to 1/5 (20c/100c).

in order to heat a bovine liver *in vitro* till 43°C by the pulsed focused ultrasound beams with an average acoustic power of 1 W, 2 W and 3 W the exposure time of 5 min, 30 s and 9 s, respectively, is necessary. It is evident from this figure that it was possible to ablate the tissue ($T > 56$°C) only using the beam with the average acoustic power of 3 W after at least 3 minutes exposure time. Figure 3 shows that for the beams with the same average acoustic power the shorter is duration of the tone bursts the higher is the temperature rise induced. The real-time monitoring of changes in the ultrasonic images of cross-section of the bovine liver samples exposed to pulsed focused ultrasound with various average acoustic power has also shown that only the beam with the acoustic power of 3 W was able to induce the necrosis area visible in the image. The dynamics of changes in the ultrasonic images of the bovine liver sample is presented in Fig. 4. The images recorded before the exposure and 2 min, 3 min and 8 min after exposure to focused ultrasound are shown.

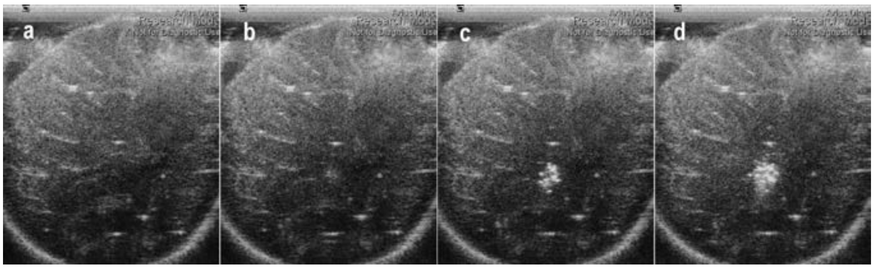

Fig. 4. Ultrasonic images of the bovine liver sample (cross-sections in the focal plane), exposed to the pulsed focused ultrasonic beam with the average acoustic power of 3 W and duty-cycle of 0.2, recorded before the exposure (a) and 2 min (b), 3min (c) and 8 min (d) after the exposure.

4. Conclusions

The temperature rise induced locally in a bovine liver *in vitro* by pulsed nonlinear focused ultrasonic fields with various acoustic properties generated from the 7-elements planar annular array transducer with electronically steered time-delay of excitation of its elements have been measured during 10 min exposure. The measurements were carried out in two-layer media comprising of a 13 mm water layer and a 20 mm layer of bovine liver. The electronic adjustment of time-delay of excitation of the transducer elements enabled guiding the focal spot of the beam at the desired 20 mm distance from the transducer. The quantitative analysis of the obtained results allowed to find the exposure time required to heat locally the bovine liver to the temperature of 43°C (applied during treatment by hyperthermia) and of 56°C (applied during HIFU treatment) for each beam with acoustic properties considered. It was found also that for the beams with the same average acoustic power the shorter is the tone burst duration the higher is the temperature rise induced (see Fig. 3). The development of the numerical model capable of predicting the temperature rises induced in tissues by pulsed focused nonlinear beams generated from the ultrasonic annular array transducers will create the possibility to control the thermal effects in tissues at various depths under the skin and will be the purpose of our further work.

The real-time monitoring of dynamics of growth of the thermo ablation area was performed using the ultrasonic imaging technique. The obtained results have shown that the necrosis area becomes visible in the ultrasonic image only for the beams with sufficiently large acoustic power. The quantitative analysis of the obtained results allowed determining both the minimal acoustic power and exposure time able to induce thermo ablation visible in the ultrasonic image. They were found to be 3 W and 3 min, respectively.

Acknowledgments

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