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Thermal effects induced in tissues by pulsed focused ultrasonic beams from annular array transducer

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Introduction. In recent years, the number of therapeutic applications of pulsed focused ultrasound beams with various intensity is steadily increasing [1]. All these applications need a knowledge of both the temporal and spatial distributions of pressure and temperature in these nonlinear beams in order to plan effective treatment with minimal level of adverse side effects. Many therapeutic applications of focused ultrasound are based on thermo ablation of detected lesions which may be located inside tissues at different depths [1]. In these cases the tumor temperature should rise above 56°C (HIFU techniques). Some treatments using pulsed focused ultrasound need the lower intensity beams to heat tissues up to 43°C (techniques based on enhancement of drug uptake or on stimulation of immune system) [1, 2]. In order to raise a tumor temperature to desired level the focal spot of the ultrasonic beam is guided to the lesion. The concentration of acoustic energy in tissues at the desired depth can be achieved using single-element circular concave piezoelectric transducers with selected diameters and radii of curvature (ROC). This solution is inefficient because it requires as many transducers as there are depths at which tumors are localized. In order to solve this problem a new approach allowing to concentrate the acoustic energy at different depths inside tissues, using a planar multi-element phased annular array transducer with electronically steered focus, was proposed. The range of biological effects induced in tumors by pulsed focused ultrasound beams depends on their acoustic properties determined by the initial tone burst frequency, average 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 beam with a 20 mm focal length and various acoustic properties generated from the planar 7-element annular array transducer with the elements having the same radiating area.

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 thermo ablation spot induced in the bovine liver *in vitro* was not visible in the ultrasonic image although there was

there in fact. After cutting the sample along the acoustic beam axis the necrosis spot was visible with the naked eye.

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

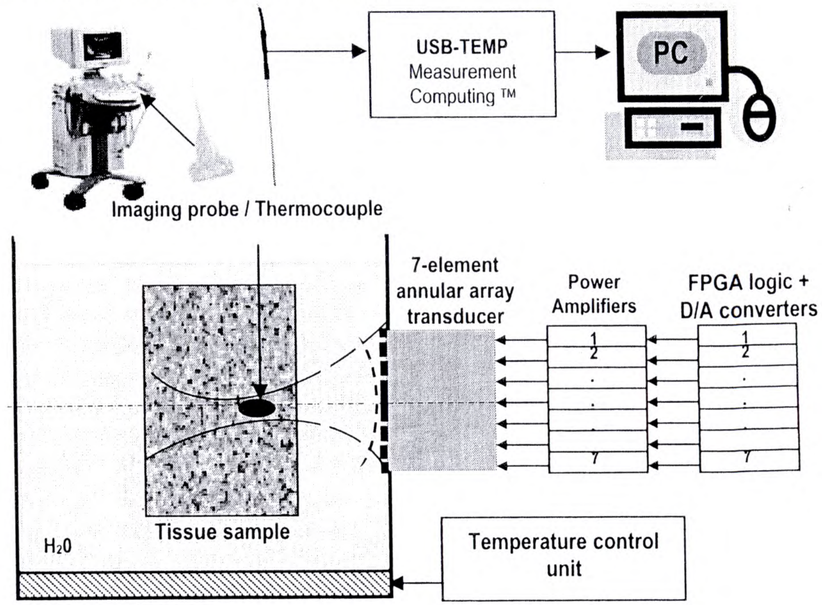

Fig. 1. Experimental setup

The acoustic pressure tone bursts were generated at the surface of the planar 7-element annular array transducer with an outer diameter of $2a_{eff} = 20$ mm and centre frequency of 2.4 MHz. Transducer was made of Pz26 ceramics (Ferroperm, Kvistgart, Denmark). All elements of the transducer had the same area to provide the uniform pressure distribution at the surface. The detailed description of the transducer design was published in [3]. The transducer was air-backed and had a quarter-wavelength matching layer. The transmission electronics were based on seven custom made broadband power amplifiers [3] controlled by seven D/A converters AD9717 and programmable logic system FPGA (Altera Aria EP1AGX). The transducer elements were driven by tone bursts with various amplitude, duration, duty cycle and time-delay to produce the focused ultrasound field with the focal plane at the desired distance. Time-delays of pulses exciting the individual elements were calculated using the Matlab 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 beam with the 20 mm focal length. 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 by two techniques: first - using the power balance and second - using the calibrated hydrophone. The measurements were carried out in water. The pressure amplitudes of the initial tone bursts and the radiating aperture apodisation 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 [4] to numerical solution of the second order nonlinear differential wave equation was used. The radial pressure variations in water were measured at the 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 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 219, 310 and 380 kPa and apodisation function $P_0(r) = P_0\,|1 - (r/a_{eff})^{10}|$. 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 purchased within 4 hours after slaughter. Each sample was degassed, inserted in a cylindrical chamber with an acoustically transparent 20 μm thick Mylar film stretched over each end and immersed in the water tank. The chamber with the 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 [5, 6] this distance is specific for each transducer with $ka >> 1$ and does not depend on the source-pressure which produces in water weak to moderate nonlinear fields. The choice of this distance was done to maximize the harmonics generation effects being one of the reasons of the temperature rise induced in tissues by focused ultrasound. The condition of weak to moderate nonlinear fields was determined in [7, 8] 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 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 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 ±0.5 mm. Due to small diameter of the thermocouple it's influence on measurement results was negligible. The temperature rise detected by thermocouple was recorded with 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 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.

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 2.4 MHz, 7-element planar annular array transducer in two-layer media comprising of a 13 mm water layer and a 20 mm layer of bovine liver *in vitro*. 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 spot 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 1W, 2W and 3W and duty-cycle of 0.2 (20 cycles/100 cycles) are shown. Plots in Fig. 2 indicate that 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. As it is evident from this figure only using the beam with the average acoustic power of 3W it is possible to lead to thermo ablation after at least 4 minutes exposure time. Fig. 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 shown that only the beam with the acoustic power of 3W 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 before exposure and 2 min, 3 min and 8 min after exposure to focused ultrasound are shown.

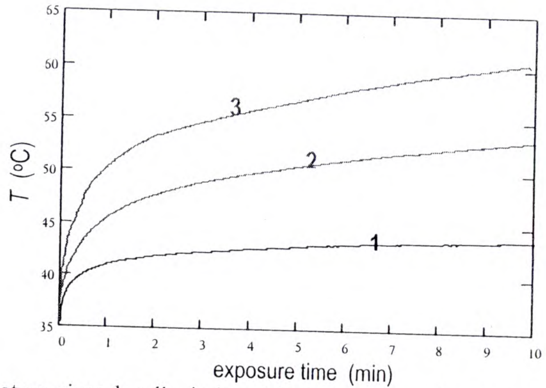

Fig. 2. Temperature rises locally induced in bovine liver *in vitro* by pulsed focused ultrasound beams with a duty cycle of 0.2 and the average acoustic power varied between 1W and 3W and measured during 10 min exposure in the beam focus.

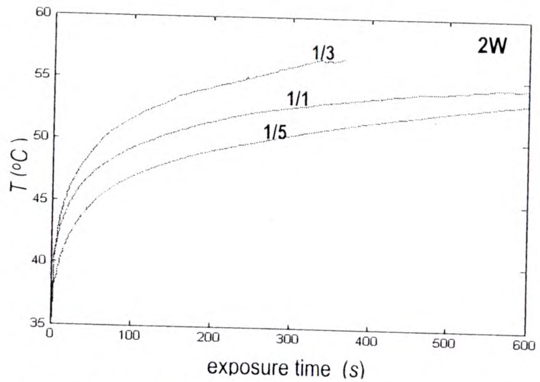

Fig. 3. Temperature rises induced in bovine liver *in vitro* by pulsed focused ultrasound beams with an acoustic power of 2 W and varied duty cycle measured during 10 min exposure time. The duty cycle was varied as follows: 1/30 (5 cycles/150 cycles), 1/15 (10c/150c) and 1/5 (20c/100c).

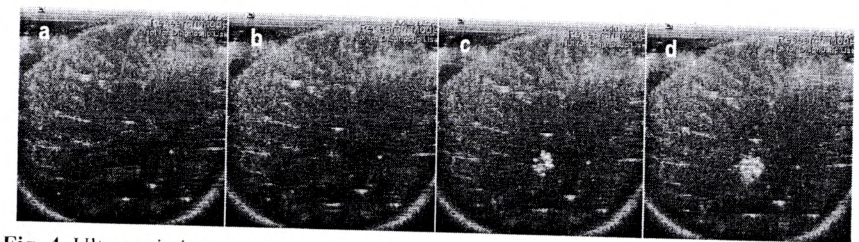

Fig. 4. Ultrasonic images of cross-section (in the focal plane) of the bovine liver sample, exposed to pulsed focused ultrasound beam with the average acoustic power of 3W and duty-cycle of 0.2, made before exposure (a) and 2 min (b), 3 min (c) and 8 min (d) after exposure.

Conclusions. The temperature rises induced locally in a bovine liver *in vitro* by pulsed nonlinear focused ultrasonic fields with various acoustic power and duty-cycle generated from the 7-element planar phased annular array transducer with electronically steered time-delay of excitation of it's elements have been measured during 10 min exposure time. The electronic steering of time-delay of excitation of the elements enabled guiding the focal spot of the beam at the desired distance from the transducer. The quantitative analysis of the obtained results allowed to find the exposure time required to heat locally the bovine liver *in vitro* to the temperature of 43°C (applied during treatment by hiperthermia) 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 bursts duration the higher is the temperature rise induced (see Fig. 3). The development of the numerical model capable of predicting of 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 has shown that the necrosis area becomes visible to the naked eye only when the acoustic power of the beam is sufficient. For the beams used the quantitative analysis of the obtained results allowed to determine that the acoustic power able to induce necrosis visible in the ultrasonic image is equal to 3 W.

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Many therapeutic applications of focused ultrasound are based on heating of a detected lesion which may be located inside tissues at different depths under a skin. In order to raise the tumor temperature the focus of the ultrasonic beam is guided to it. The focusing of acoustic energy in tissues at the desired depth can be achieved using single-element circular concave piezoelectric transducers with the selected diameters and radii of curvature. This solution is inefficient because it requires as many transducers as there are depths at which tumors are localized. In order to solve this problem a new approach, allowing to concentrate the acoustic energy at different depths inside tissues using a planar multi-element annular array transducer with electronically steered time-delay of excitation of its elements, was proposed in this work. The main purpose of this study was to investigate the thermal fields induced in bovine liver *in vitro* by the pulsed focused ultrasound beam with various acoustic properties generated from the planar multi-element annular array. The array with 20 mm outer diameter and 2.4 MHz centre frequency has 7 elements with the same radiating area. The electronic steering of the time-delay of excitation of each element allowed to obtain the focal spot of the beam at any distance from the transducer surface. This paper presents measurement results performed for the beam focused at 20 mm distance. In order to maximize nonlinear propagation effects being one of the reasons of the local temperature rise induced in tissues by focused ultrasound the measurements have been performed in two-layer parallel media of propagation comprising of a water layer whose thickness was specific for the transducer used and equal to 13 mm, and of a bovine liver *in vitro* layer with a thickness of 20 mm. The thickness of water layer was determined numerically as the axial distance at which the second harmonics amplitude for the tone burst generated by the transducer used in water starts to increase rapidly. The measurements of temperature rises *versus* time were performed using a thermocouple placed inside the liver at the beam focus. The temperature rises induced in the bovine liver *in vitro* for beams with the average acoustic power of 1W, 2W and 3W and duty cycle of 1/5, 1/15 and 1/30 have been measured. For each beam the exposure time needed for local heating of the liver to a temperature of 43 °C (used in therapies based on ultrasonic enhancement of drug delivery or therapies involving stimulation of immune system by enhancement of the heat shock proteins expression) and to a temperature of 56 °C (used in HIFU therapies) was determined. In each sample of liver for each considered beam at first, the measurement of temperature rise (with thermocouple) was carried out, and then, exposing the sample (without thermocouple) to the same beam the real-time monitoring of dynamics of the thermo ablation area growth was performed using the ultrasonic imaging technique. The necrosis area becomes visible in the ultrasonic image only when the beam has sufficient acoustic power. The quantitative analysis of the obtained results allowed to determine the beam acoustic power and exposure time that are sufficient to visualize necrosis spot in the ultrasonic image.

Complex evaluation of elasticity of human common carotid artery

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Introduction. The early diagnosis and treatment is the key aspect for the reduction of mortality from various cardiovascular diseases. The state of human common carotid artery is believed to be of great importance, because it's one of the major sites where pathologies emerges and develops. Artery wall or intima-media thickness (IMT) is one of the few parameters, which undoubted correlation with cardiovascular diseases is determined in clinical trials. However, clear changes of IMT are often detected, when pathology is already reached complicated and irreversible state. On the other hand, it's believed that elasticity parameters, i.e. compliance, elasticity modulus and etc., alter before artery morphology parameters, such as IMT or lumen/wall ratio. Thus, evaluation of elasticity parameters can help to diagnose artery pathology in its early stage. Non-invasive *in vivo* methods are preferred in clinical practice, especially, in every day diagnostic examination. Ultrasound images fulfil above mentioned requirements. However, different nature, i.e. structural and physiological, elasticity parameters correlate with cardiovascular diseases differently, sometimes even conversely. Supposedly, complex evaluation, i.e. assessment of different nature elasticity parameters, enables to acquire more clear and valuable diagnostic information.

The purpose of this study is to develop methods for the *in vivo* complex evaluation of diagnostic elasticity parameters of human common carotid artery employing non-invasive ultrasound images.

Methods. Proposed methods enable to evaluate two groups of important elasticity parameters – compliances and elastic modulus (Fig. 1). Main input parameters for the methods are determined using non-invasive ultrasound images. Blood flow is derived from blood velocity (v) and internal artery radius (r) measurements, performed in D-mode and M-mode ultrasound respectively. Previously proposed algorithm is employed to detect artery radius time function and relevant diagnostic parameter – IMT [1]. Typical sphygmomanometer calibrated carotid artery blood pressure time function is used to estimate compliances and classic elastic modulus.

For the assessment of compliance, contrary to classical two element Windkessel model, original four element hemodynamical model has been proposed (Fig. 2. A). Non-linear, pressure-dependent character of the compliance, which reflects artery's ability to distend and contract after pressure change, is assessed:

$$C_{P4}(P(t)) = a \cdot e^{-b \cdot P(t)}, \qquad (1)$$