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Non-invasive imaging of thermal fields induced in soft tissues *in vitro* by focused ultrasound using analysis of ultrasonic echoes displacement

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Introduction. In modern medicine ultrasound (US) has many applications such as ultrasonic imaging of selected organs, their therapy and surgery [1]. For diagnostic applications the ultrasound exposure levels are chosen low to be able to give images with good spatial and temporal resolution using pressures sufficient to get an acceptable signal-to-noise ratio SNR, safe for patient. The aim of diagnostic ultrasound is to obtain the required information without causing adverse cellular effects. In contrast, therapeutic or surgical applications require that the exposured tissue lesions were subjected to reversible or irreversible changes depending on the target of treatment. Therapeutic ultrasound energy is usually delivered as pulsed waves focused inside tissues in the localized tumor. The main goal of many therapeutic applications of ultrasound is tissues heating. The efficacy of therapy depends on precision of acoustic energy level supplied to the desired target inside tissues, i.e. on precision of temperature rise induced. Monitoring of the temperature rise induced in tissues by focused ultrasound during treatment becomes a necessity. Currently the most popular method of imaging of local thermal fields induced in tissues by therapeutic ultrasonic beams is Magnetic Resonance Imaging (MRI). For example, MRI-guided High Intensity Focused Ultrasound (HIFU) therapy allows to control the temperature rise inside tissues opening opportunities for new therapeutic applications [2].

The main disadvantage of combination of these two modalities (US + MRI) limiting possibilities of applications is high costs of the MRI technique. Our objective was to develop an alternative method based on diagnostic US modality for temperature control inside tissues heated locally by focused ultrasonic beams. Several methods are known for non-invasive estimation of the temperature rise induced in tissues by focused US. One of them is based on signal processing of the backscattered ultrasonic echoes which are changing with a change of the acoustic parameters of tissues during heating (thermo-acoustic coupling). For example, the method described in publication [3] is based on an analysis of the average grey-scale level of the B-mode image related to the scattering coefficient. Echo Strain Estimation (ESE) algorithm analyzing echoes displacement, caused by changing of the wave propagation velocity during tissues heating, is published in [4]. Another method is based on detection of the instantaneous changes in frequency [5]. In this work the ESE

method was applied for estimation of the temperature rise induced in beef liver *in vitro* by pulsed focused ultrasonic beam with the acoustic power of 2.1 W.

Materials and methods. All measurements were carried out at 36 °C in the measurement setup shown in Fig. 1.

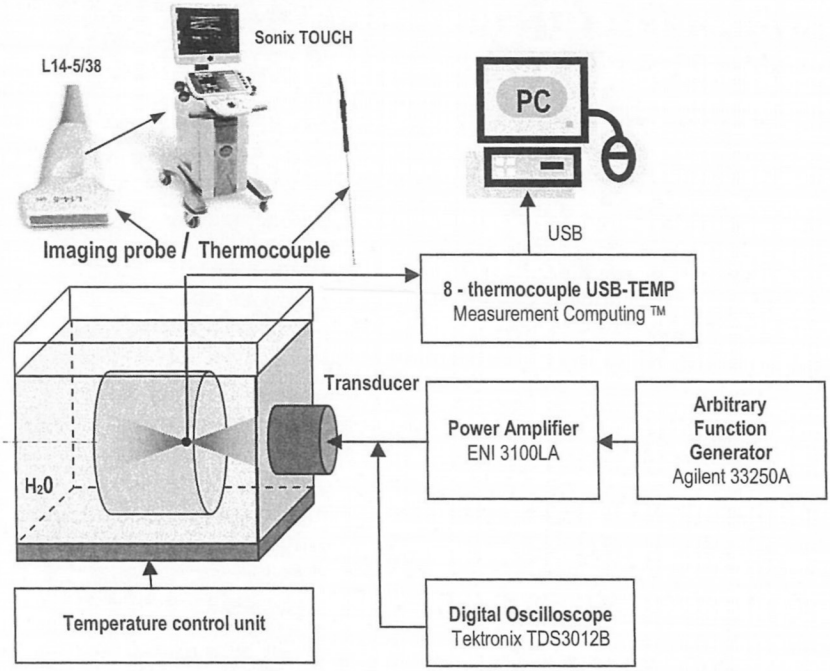


Fig. 1. Block-scheme of the experimental setup

The acoustic pressure tone bursts were generated at the surface of the PZT (Pz26, Meggitt, Denmark) circular focused transducer with a 2 MHz resonance frequency, 15 mm diameter and 25 mm radius of curvature. The transducer was air-backed, had a quarter wavelength matching layer and was driven at its resonance frequency by 20-cycle tone bursts with a duty-cycle of 0.2. The transmission electronics were based on an arbitrary function generator (Agilent 33250A, Colorado Springs, USA) that defined both the frequency and pulsing mode of tone bursts generated. Then the signal was amplified with a power amplifier (55 dB gain) ENI 3100LA (ENI, Rochester, NY, USA). The tone burst waveform was displayed with a Tektronix TDS3012B digital storage oscilloscope (Tetkronix, Beaverton, USA). The output of the amplifier excited the PZT transducer to produce the ultrasonic field. The transducer was mounted in a water tank with controlled temperature. The source pressure was determined by two methods. First, using a calibrated needle hydrophone S/N 1661 (Precision Acoustics, Dorchester, UK) with the active element diameter

of 0.2 mm and next, using a power balance (Ohmic Instruments UPM-DT-1E, Easton, USA). The source pressure used was found to be 0.37 MPa (average acoustic power of the beam used was equal to 2.1 W).

All tissue samples being tested were obtained from a slaughterhouse. Experiments were done within 8 hours after slaughter. Each tissue sample were degassed and inserted in a cylindrical chamber (with a diameter of 30 mm and height of 20 mm). The chamber had a 20 - μm thick, transparent for sound, polyethylene foil stretched over each end and was placed in a water tank. In order to maximize nonlinear effects (generation of harmonics) induced in tissues by high intensity focused beams the distance between the transducer and a water/tissue interface was selected on a basis of numerical simulations of nonlinear propagation for tone bursts generated from the transducer used and propagating in water. This distance was selected as a distance from the source at which the amplitude of the second harmonic component begins to grow rapidly. For the transducer used this distance was found to be 15 mm. In previous publications [6 - 8] it was shown that for circular sources with $ka >> 1$ (k is the wave number, a denotes transducer radius) generating weak or moderate nonlinear fields in water the axial distance, at which sudden growth of the amplitude of the second harmonic component begins is constant regardless of the source pressure.

The temperature rise induced in tissues by pulsed focused ultrasonic beam was measured in the beam focus by a thermocouple with a diameter of 0.2 mm. It was inserted in the tissue sample at the beam focal spot using thin, 0.5 mm diameter hypodermic needle fixed on the tank cover in order to ensure precise position at the acoustic beam focus. The uncertainty of position of the thermocouple tip was ± 0.2 mm. Due to small diameter of the thermocouples their influence on measurement results were negligible. The temperature rise detected by each 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 curves of the temperature rise *versus* time $\Delta T(t)$ the software TracerDAQ was used.

The temperature rise induced in the tested tissue sample by the pulsed focused ultrasonic beam generated from the transducer used is shown in Fig. 2.

For imaging the temperature rises induced inside the tissue sample by the high intensity focused ultrasonic beam the ultrasonic imaging system Sonix TOUCH (Ultrasonix, British Columbia, Canada) equipped with the linear array probe L14-5/38 operating at the 10 MHz frequency was used. The system has an access to the RF echo-signals creating the image from the selected plane of the tested tissue sample. The RF echoes were recorded from each line in the focal plane of the focused beam. The signal processing was done in the environment of the software package Matlab (Mathworks Inc., Natick, Massachusets, USA). A processing of the recorded RF waveforms to the temperature map was done using the ESE method. This method is based on the relationship between the sound velocity in tissues and their temperature. Fig. 3

shows the principle of this method. The acoustic properties of the tissue local area heated by the focused ultrasonic beam are changed and as a result the return time of ultrasonic echoes from structures located behind this area is also modified. The comparison of signals recorded before and after temperature change allowed to evaluate the echoes displacement and thus to calculate a local change of the sound velocity in tissues and to estimate their temperature rise.

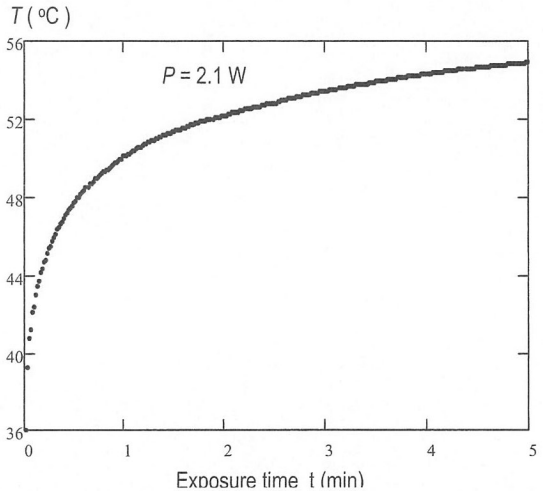


Fig. 2. Temperature rise induced in a beef liver *in vitro* by the pulsed focused ultrasonic beam with the average acoustic power of 2.1 W and measured by thermocouple at the beam focal spot during 5 min exposure.

A signal processing algorithm is presented in Fig. 4. First, the algorithm involves the frequency band filtration that removes noise originated from the heating transducer thereby improving the SNR. Then, the processing involves detection of a phase shift of the echoes recorded from the same line of the subsequent images. In our case the phase shift of the complex signal obtained by the Hilbert transform was detected. The obtained data were then subjected to the low-pass filtering in order to smooth the results for preparing them to the following differentiation procedure. The change of the sound velocity in tissues was calculated by the following formula:

$$\Delta c(x,z) = c \cdot \frac{f_S}{f_N} \cdot \frac{\Delta\varphi(x,z) - \Delta\varphi(x,z-1)}{2\pi}, \tag{1}$$

where c is the average sound velocity in tissues assumed for processing, f_S denotes the sampling frequency, f_N is the operating frequency of the imaging mode, x and z are the coordinates of each image pixel in the lateral and axial direction, respectively, $\Delta\varphi$ is the phase shift between the signals before and after heating.

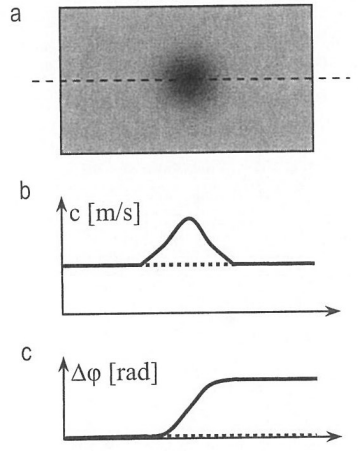


Fig. 3. Illustration of a principle of the ESE method: a) image of the tissues structure with heated area and the line of scan creating image; b) sound velocity modified by temperature; c) phase shift of the signal along the selected scan line

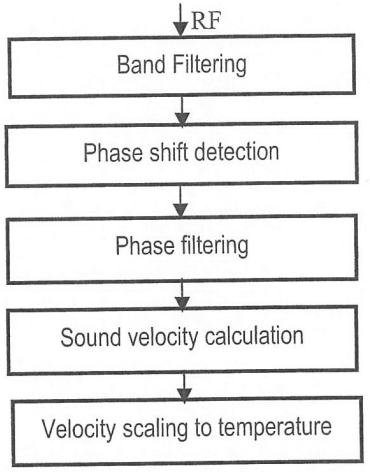


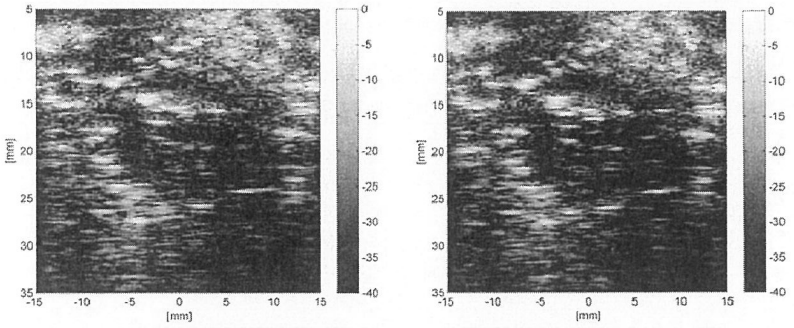
Fig. 4. Block-scheme of the algorithm used for estimation of temperature fields induced in tissues by focused ultrasound using the Echo-Strain Estimation method

Knowing what is the distribution of changes in the sound velocity the temperature field can be calculated using the relationship between these two values. Unfortunately, this relationship is not clearly specified, different types of tissues are characterized by different relationships between the temperature T and sound velocity c [4].

So, at the present stage of investigations the scaling of the results to the values expressed in Celsius degrees (°C) is only approximate, accomplished on the base of the invasive measurements carried out by the thermocouple.

Results. The temperature rise *versus* time measured by means of the thermocouple in the focal spot of the acoustic beam used is shown in Fig. 2. The obtained results allowed to assess the heating process in tested tissues and were the reference data for determining the temperature field by the non-invasive imaging technique. It is evident from Fig. 2 that an exposure of tested tissues to focused ultrasound with an acoustic power of 2.1 W may lead to the local temperature rise of about 54 °C during 5 minutes. However, this time was not sufficient to observe any visual effects showing changes in the tissue structure in the B-mode images (see Fig. 5). Only the results of the RF data processing by means of the described algorithm clearly show changes in the temperature distribution in relation to the situation before heating (see Fig. 6.). In the reconstructed temperature map an artifact in the form of a shadow behind a heated spot appeared. In the future work an attempt to remove the reasons of

its formation and to improve the presented algorithm will be undertaken. Moreover, more precise scaling and verification of the algorithm will be done.



a) b)

Fig. 5. Ultrasonic B-mode images of the heated tissue area: a) before and b) after 5 min exposure to focused ultrasound

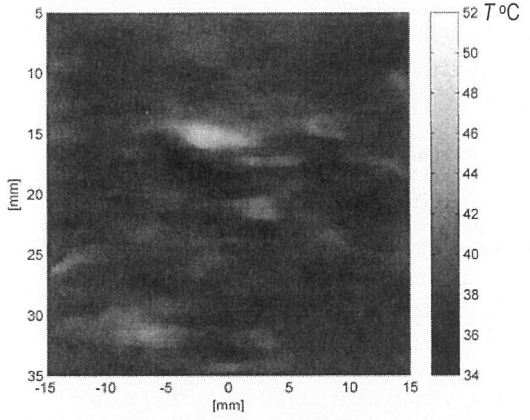


Fig. 6. Map of the temperature distribution in the beam focal plane

Conclusions. It should be noted that the presented results are preliminary data for studying the non-invasive ultrasonic measurements of temperature rises in tissues induced by the high intensity focused ultrasound (HIFU). Despite of some imperfections of the presented algorithm the results are promising to realize non-invasive monitoring of the temperature fields during treatment based on thermal effects.

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Therapeutic and surgical applications of focused ultrasound require monitoring of local temperature rises induced inside tissues. From an economic and practical point of view ultrasonic imaging techniques seem to be the best for a temperature control. In this work an attempt to apply the method of the ultrasonic echoes displacement estimation for monitoring local temperature rises in tissues during their heating by focused ultrasound is presented. The estimated temperature rise was compared with this measured by a thermocouple. The obtained results enable to evaluate the temperature fields induced in tissues by pulsed focused ultrasonic beams using non-invasive imaging ultrasound technique.