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Heating of tissues *in vivo* by pulsed focused ultrasound to stimulate enhanced HSP expression.

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Abstract. The main aim of this work was numerical modeling of temperature fields induced in soft tissues *in vivo* by pulsed focused ultrasound during neurodegenerative disease treatment and experimental verification of the proposed model for a rat liver. The new therapeutic approach to neurodegenerative diseases consists of stimulation of enhanced expression of the Heat Shock Proteins (HSP) which are responsible for immunity of cells to stress. During therapy the temperature rise in tissues *in vivo* should not exceed 6 °C above level of the thermal norm (37 °C). First, the 3D acoustic pressure field, and the rate of heat production per unit volume due to that field, were calculated using our 3D numerical solver capable of predicting nonlinear propagation of pulsed high intensity waves generated from circular focused acoustic sources in multilayer configuration of attenuating media. The two-layer configuration of media (water - rat liver) assumed in calculations fairly well approximated both the real anatomic dimensions of rat liver and the geometric scheme of our experimental set-up. A numerical solution of the Pennes bio-heat transfer equation which accounted for the effects of heat diffusion, blood perfusion and metabolism rates, was employed to calculate the temperature fields induced in the rat liver by the ultrasonic beam. The numerical simulation results were verified experimentally using a thermocouple inserted in the liver of a rat under anesthesia at the beam focus. The quantitative analysis of the obtained results enabled estimation of the effects of several acoustic and thermal parameters of the rat liver *in vivo* on the temperature rise, as well as determination of exposure time for ultrasonic beams with varied acoustic power generated by a 2-MHz circular transducer of 15-mm diameter and 25-mm focal length, in order to avoid the tissue overheating that leads to cells necrosis, which would be unacceptable in neurodegenerative disease treatment.

Keywords: low power ultrasound, tissue heating, HSP expression enhancement, cells immunity, degenerative deceases treatment.
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INTRODUCTION

Recent investigations, reviewed in [1], have shown that exposure of tissues to ultrasound may lead to enhanced HSP expression. The essence of the proposed therapeutic application of ultrasound is targeted local tissue heating using low intensities as long as the temperature reaches 43 °C. Raising the temperature above the physiological norm of 37 °C by no more than 6 °C may have a number of beneficial physiological effects, among others enhanced HSP expression, or an increase in the blood supply to the affected area.

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NUMERICAL METHODS

The planar circular transducer with a centre frequency f_0 and radius a is located in the cylindrical coordinate system as shown in Fig. 1. The plano-concave PMMA lens is used in conjunction with the transducer to produce a focused field and to bring the focal plane to the chosen axial distance F from the transducer face.

The transducer is immersed in water and generates tone bursts with the centre frequency f_0, intensity I_0, pulse duration Δt and duty cycle d. The acoustic waves pass through water and penetrate a rat liver. The acoustic beam axis is perpendicular to the water – rat stomach interface. The rat stomach area covering liver is located at the specific axial distance z_1 from the transducer face. In a previous publication [2] it was shown that, for circular acoustic sources which are many wavelengths across ($ka >>1$) and which produce in water weak to moderate nonlinear fields the axial distance z_1 at which sudden growth of the second harmonics occurs is specific for each source and is independent of the source pressure. The weak to moderate nonlinear fields in water mean that the shock formation distance is in the transition or far field regions of the sound beam, i.e. the ratio of the shock formation distance l_D to the Rayleigh distance R_0 is larger than 0.3 [3].

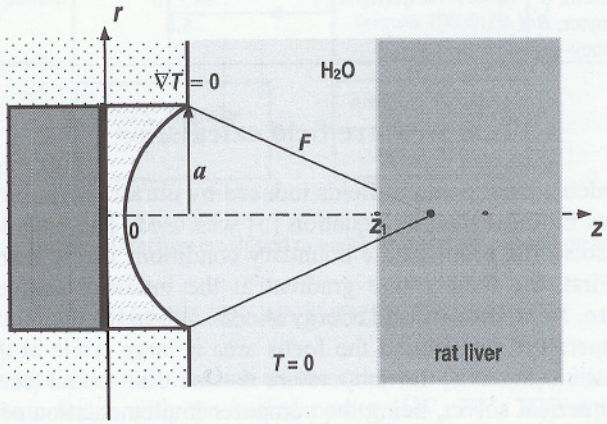

FIGURE 1. Geometric scheme for calculation of the pressure and temperature fields induced in the two-layer configuration of media: water - rat liver by circular focused transducer considered.

Acoustic pressure field calculation

In order to calculate the pulsed nonlinear acoustic pressure fields generated by axisymmetric sources in multilayer attenuating media with arbitrary frequency-dependence power law of attenuation as well as the rate of heat deposition per unit volume due to these fields, an original 3D numerical solver, recently developed in our lab, was used. The solver is a computer implementation of the numerical model based on the TAWE approach [4] to the numerical solution of the second order nonlinear differential wave equation for acoustic sources with axial symmetry. The model requires a number of input parameters that characterize the boundary conditions of the source and media of propagation. The source parameters required for the model are:

diameter, focal length, pressure amplitude on the surface, apodisation function of radiating aperture, initial tone burst centre frequency, duration, envelope function and duty cycle. The source parameters used for calculations were measured in water and are presented in Table 1. The media parameters required for the model are: density, sound velocity, attenuation coefficient and its frequency-dependence law, nonlinearity parameter. The acoustic parameters for media of propagation used in the numerical model are given in Table 2.

TABLE 1. The values of the source parameters used in the numerical model

Effective radius a (mm)	**Focal length** F (mm)	**Centre frequency** f_0 (MHz)	**Source pressure** P_0 (MPa)	**Focusing gain** G	**Pulse duration** (cycles)	**Duty cycle** (%)
7.5	25	2	0.131 ÷ 0.226	9.4	8	20

TABLE 2. The values of acoustic parameters of media at 37 °C temperature used in numerical model.

Medium parameters		**Water**	**Rat liver**
Density, ρ	kg/m^3	993	1060
Sound velocity, c	m/s	1524	1615
Attenuation coefficient, α	Np/(m· Hz^b)	$1.44 \cdot 10^{-14}$	$(7 \div 9) \cdot 10^{-6}$
Nonlinearity parameter, B/A		5.6	7
Attenuation frequency-dependence index, b		2	1 ÷ 1.12

Temperature field calculation

In order to calculate temperature fields induced by ultrasound in biological tissues *in vivo* the Pennes bio-heat transfer equation [5] was used. The equation was solved numerically. To solve the problem the boundary conditions of the thermal insulation were assumed. First, the temperature gradient at the interface source – water was assumed to be zero. Next, the acoustic energy is concentrated at the focus of the beam, therefore the temperature rise around the focus area is large while at the peripheries, far from the acoustic beam axis, the temperature rise is infinitesimal (see Fig. 1).

An original numerical solver, being the computer implementation of the numerical model, capable of predicting temperature fields induced in multilayer biological media by pulsed focused ultrasound beams, was developed. The model requires a number of input parameters that relate to the thermal properties of media. The media thermal parameters required for the model are: heat capacity, thermal conductivity, perfusion rate of blood. The values of these parameters for water are well documented in the literature and for the rat liver were varied in the range quoted in Table 3 in order to fit the numerical simulation results to the experimental data.

TABLE 3. The values of the media thermal parameters used in numerical model.

Medium parameters		**Water**	**Rat liver**
Specific heat	J/(kg · °C)	4200	3500 ÷ 3600
Thermal conductivity	W/(m · °C)	0.63	0.2 ÷ 0.5
Perfusion rate of blood	kg/(m^3 · s)	0	0.5 ÷ 0.9

MATERIALS AND METHODS

A block diagram of the experimental facility used for measuring the temperature fields induced in rat liver *in vivo* by pulsed focused acoustic beams is shown in Fig. 2.

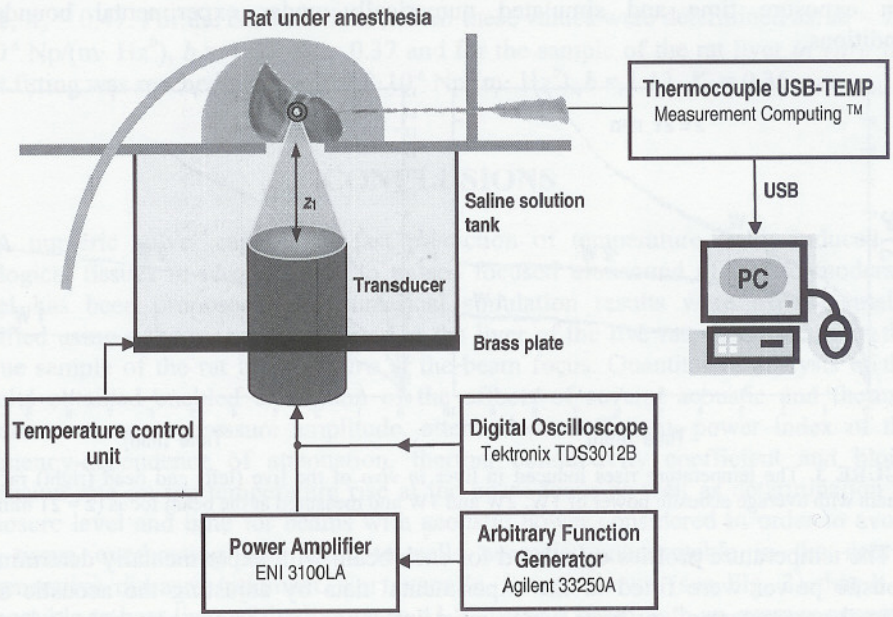

FIGURE 2. The experimental facility employed to make temperature measurements.

RESULTS AND DISCUSSION

The temperature rises *versus* time in the rat liver *in vivo* irradiated by the pulsed focused ultrasonic beam with the varied power (1W, 2W, 3W) were measured and compared with those measured in the fresh rat liver sample for the same ultrasonic regime as well as with those simulated numerically under experimental boundary conditions. The calculated results were fitted to the experimental data by adjusting the acoustic and thermal parameters of the rat liver: absorption coefficient, its frequency-dependence power law, specific heat and thermal conductivity. The best agreement between the results predicted numerically and the experimental data determined the values of those parameters.

Figure 3 illustrates the temperature elevations induced in liver *in vivo* of the live and dead rat by the pulsed ultrasonic beams with average power of 1W, 2W and 3W measured *versus* time at the beam focus. It is evident from Fig. 3 that temperature rises *versus time* for liver of the live rat are smaller than for the dead rat. Furthermore, the difference between those rises increases with increasing exposure level and time. A number of factors could be responsible for this. It is possible that heat loss in the liver of the live rat are caused by blood perfusion. It is also probable that soft tissues *in vivo*

in live organisms have different acoustic and thermal properties from those in dead organisms *in vivo* or from those in samples of fresh organs extracted from these organisms. Figure 4 shows the temperature rises, induced in liver *in vivo* of the alive and dead rat as well as in liver *in vitro* of the fresh rat liver sample by the pulsed ultrasonic beam with average power of 1W, measured at the beam focus during 10-min exposure time and simulated numerically under experimental boundary conditions.

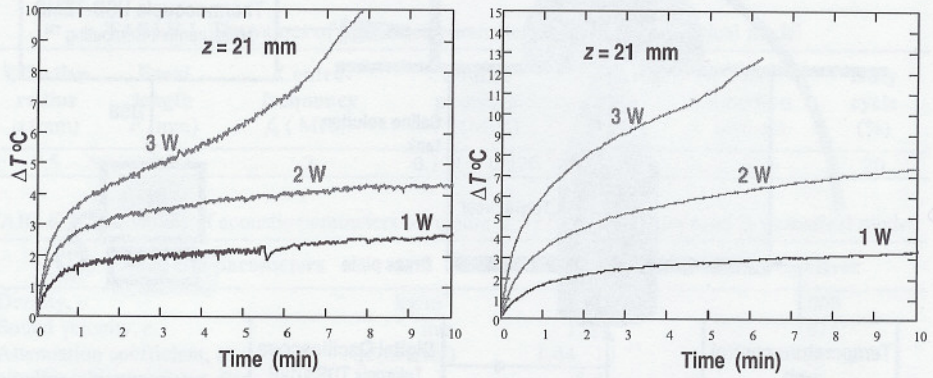

FIGURE 3. The temperature rises induced in liver *in vivo* of the live (left) and dead (right) rat by a beam with average acoustic power of 1W, 2W and 3W and measured at the beam focus (z = 21 mm).

The temperature profiles calculated for each beam with experimentally determined acoustic power were fitted to the experimental data by adjusting the acoustic and thermal parameters of rat liver which most influence the temperature rises induced: attenuation coefficient, α_1, its frequency-dependence power index, b, and thermal conductivity coefficient, K_s.

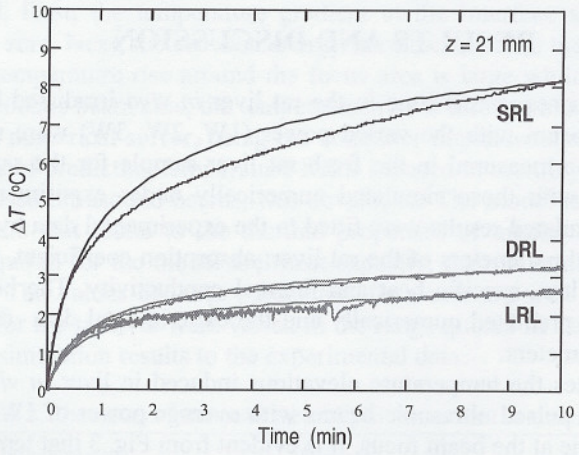

FIGURE 4. Temperature rises induced in liver *in vivo* of the anaesthetized live (LRL) and dead (DRL) rat as well as in the sample of the fresh rat liver *in vitro* (SRL) by the pulsed focused beam with acoustic power of 1 W, measured (points) at the beam focus (z = 21 mm) during 10-min exposure and simulated numerically (solid lines) under experimental boundary conditions.

The best agreement between the obtained theoretical results and experimental data enabled the determination of values of those parameters for the rat liver *in vivo* (alive and dead) and for the rat liver sample *in vitro*. In the case of a beam with 1W average acoustic power the best correlation between the numerical and measurement results for the live rat liver *in vivo* was obtained with values: $\alpha_1 = 7.8 \cdot 10^{-6}$ Np/(m· Hz^b), $b = 1.02$, $K_s = 0.47$. For the dead rat liver *in vivo* these values were determined as: $\alpha_1 = 7.8 \cdot 10^{-6}$ Np/(m· Hz^b), $b = 1.02$, $K_s = 0.37$ and for the sample of the rat liver *in vitro* the best fitting was reached with: $\alpha_1 = 7.8 \cdot 10^{-6}$ Np/(m· Hz^b), $b = 1.12$, $K_s = 0.36$.

CONCLUSIONS

A numeric solver capable of fast prediction of temperature fields induced in biological tissues *in vivo* exposed to pulsed focused ultrasound of low to moderate level has been proposed. The numerical simulation results were experimentally verified using a thermocouple inserted in the liver of the live rat, dead rat and in the tissue sample of the rat liver *in vitro* at the beam focus. Quantitative analysis of the results obtained enabled estimation of the effects of several acoustic and thermal parameters: source pressure amplitude, attenuation coefficient, power index of the frequency-dependence of attenuation, thermal conductivity coefficient and blood perfusion rate on the temperature rise at the beam focus as well as determination of exposure level and time for beams with acoustic power considered in order to avoid the tissue overheating that leads to cells necrosis, unacceptable in the neuro-degenerative diseases treatment. For example, it was shown (see Fig. 3) that it is impossible to heat liver of the live rat to 43 °C using a beam with an average acoustic power of 1W or 2W. But using the beam with acoustic power of 3W the exposure time should not exceed 4 min.

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