SECTION II. MEDICAL SCIENCES

Gryzunov V.V., Tkhai D.V., Kim Yu.V., Nersesyan A.A.

Dosimetric phantom for evaluation of the heat flows distribution under HIFU-exposure at the stage of selecting a therapy

*Pavlov First Saint Petersburg State Medical University
(Russia, Saint Petersburg)*

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Abstract

New technologies and methods designed to reduce the risk and magnitude of surgical manipulations are being actively introduced into clinical practice, one of which is the method of high-intensity focused ultrasound (HIFU) thermoablation. However, it is quite difficult to assess the spatial distribution of acoustic and thermal fields when selecting a therapy scheme. To simulate the architectonics of the treatment area it is proposed to use a dosimetric phantom. The pattern of changes in the phantom in the heat-affected zone is shown with an ultrasound scanner in real time, which allows to visualize structural changes in the area of thermal destruction and verify the dosimetric plan of ultrasound therapy.

Keywords: high-intensity focused ultrasound, tissue-equivalent phantom, thermal field, thermoablation, planning, dosimetry.

The clinical practice of oncologic surgery is actively introducing high-tech treatment methods designed to significantly limit the invasiveness and extent of surgical manipulations, one of which is the use of high-intensity focused ultrasound (HIFU). The HIFU method has a number of significant advantages over traditional methods of treatment (noninvasiveness, repeatability until a positive clinical effect is achieved, absence of post-procedural changes in healthy tissues, etc.), which reduces the degree of risk and lays the foundation for the development of minimally invasive, organ preserving oncologic surgery [1].

For successful application of HIFU therapy in patients, it is necessary to determine the optimal characteristics of high-intensity focused ultrasound and thermal destruction schemes in each case at the treatment planning stage. To solve these problems, it is advisable to simulate the distribution of acoustic and thermal fields depending on the amplitude, frequency, intensity, exposure and geometry of the transducer, as well as taking into account the absorption and refraction of ultrasound and heat diffusion in the media. But it is not always possible to measure basic parameters of field distribution in biotissues. Even creation and use of HIFU procedure control systems with ultrasound and NMR tomography monitoring in real time allows only to react promptly to tissue changes resulting from thermoablation in the focus of exposure. Unfortunately, development of HIFU-treatment algorithms for each specific case based on clinical trials using unique engineering developments are extremely expensive and not always justified procedures. And the issues of standardization and dosimetry in the use of high-intensity focused ultrasound remain very relevant.

Therefore, experimental modeling of HIFU exposure modes on the phantom at the stage of dosimetric planning before therapeutic application of ultrasound in each case is of great importance in clinical conditions.

The aim of the work is to choose dosimetric phantom, which would reproduce biophysical characteristics of the living tissue, to develop exposure modes models of high-intensity focused ultrasound and evaluate possible mechanical and thermal effects under certain characteristics of HIFU-therapy.

Based on the analysis of the initial data, the main requirements for the dosimetric simulator model were formulated to optimize the ultrasound exposure for a particular application, namely:

- multiplicity of use of the phantom during HIFU exposure, which reduces the overall cost of the technological process at the planning stage;

- the basic biophysical parameters should be comparable to biological tissues;
- possibility of visualization and ultrasound location of the thermal destruction focus;
- ability to perform thermometry in the dosimetric phantom in real time mode during HIFU-effect.

Material and methods. When choosing a phantom, the following acoustic parameters were considered (sound velocity, attenuation coefficient, backscatter coefficient), thermal characteristics (heat capacity and thermal conductivity), mechanical properties (elasticity). According to the totality of these properties, they should imitate biotissues as much as possible. Particular attention was also paid to the transparency of the material for visualization of HIFU effects. The materials based on polyacrylamide gel (PAG) turned out to be the closest to biological tissues in terms of a number of acoustic and mechanical properties (Table 1) [2-3]. Of the general range of PAG, Phantom PAG-3 was preferred.

Table 1

Comparison of mechanical properties of PAG-3 phantom and liver tissue

<i>Object of comparison</i>	<i>Density (kg/m³)</i>	<i>Shear modulus (kPa)</i>	<i>Young's modulus (kPa)</i>
<i>Liver tissue</i>	<i>1060,0±10,0</i>	<i>3,5±0,55</i>	<i>13±0.30</i>
<i>PAG-3</i>	<i>1057,0±13,0</i>	<i>4,55±0,33</i>	<i>10,63±0,93</i>

To assess mechano-thermal HIFU-associated effects in phantoms we used a modular stand including ultrasound diagnostic scanner "Angiodin-1" (firm "Bioss"), and installation consisting of a transmitter generating focused ultrasound of high intensity, movable module "Diather". Flat-concave transducer H-148 S/N 010 (Sonic Concepts, Inc., USA) with central frequency of vibration generation 2.5 MHz (minimal frequency 1.4 MHz), active diameter 64 mm and central aperture 20 mm were used as ultrasonic generator. The transmitter with concave surface created local high-energy impact in the spot area up to 0.6 mm. Degassed water in a glass vessel, where the transmitter and phantom were placed, was used to allow the ultrasonic waves to pass through.

Four thermosensors in PVC sealed tubes of a digital multi-channel thermograph (T-8) were pre-injected into the PAG-3 phantom at different distances from the focus to assess the thermal pattern.

The phantom was placed in a plastic container with temperature-sensitive sensors in a glass vessel filled with degassed water, and an ultrasound scan of the PAG-3 was performed (Figure 1).

Figure 1. Ultrasound image of a tissue-equivalent phantom in a glass vessel filled with degassed water

Research results. 22 phantoms were subjected to 8.2 kW/cm^2 and 23.3 kW/cm^2 ultrasound in a focal spot of up to 0.6 mm diameter with different exposures and temperature estimates in the spatial zones of the HIFU-induced thermal pattern. The results obtained are shown in figures 2 and 3.

Figure 2. Temperature sensor readings at different distances from the thermal degradation zone at 8.2 kW/cm^2 HIFU intensity and a single exposure

Figure 3. Temperature sensor readings at different distances from the thermal degradation zone at HIFU intensity 23.3 kW/cm^2 and a single exposure

The data obtained indicate a directly proportional relationship between exposure and temperature in the near ($p < 0.001$) and far ($p > 0.05$) perifocal zones. There was no significant temperature increase in the far zones, which indicated a limited thermoablation zone and predetermined the expediency of assessing the temperature increase in the perifocal zones (Table 4) and calculating the integrated value of the increment depending on the difference of temperature increase in the near zone of HIFU (ΔT) and the temperature gradient (Δt) in the far perifocal regions.

For this purpose, the average initial temperature of the phantom was determined, which was 20.1 °C, and for each spot of HIFU treatment, the value of temperature increase was estimated. Subsequently, it was compared with the temperature gradient of the near and far zones. It was found that with increasing temperature increment in near zone (ΔT_{Co}), the temperature gradient increment (Q) shows opposite tendency, which value reflects the relation between temperature increment in near zone and temperature difference in far zone (Δt °C). This trend is most pronounced between 150 and 1000 ms (Table 2), indicating the phenomenon of heat energy accumulation in the focal zone of the phantom.

Table 2

Temperature rises in focus and incremental temperature gradient

№	HIFU shot exposure, ms	Temperature increases relative to the reference value (ΔT_{Co})	Temperature difference (Δt °C)	Magnitude of the temperature gradient increment (Q)
1	150	25,8	4	6
2	200	29,3	4,3	6,8
3	250	34,3	4,3	7,9
4	300	40	4,3	9,3
5	350	46,6	4,4	10,5
6	400	50,3	4,6	10,9
7	450	54,5	4,9	11,12
8	500	60,5	5,1	11,8
9	1000	82,9	5,4	15,3

The temperature increase in the focal zone during repeated HIFU exposures was investigated to determine the effect of heat accumulation. The following exposure mode was chosen for the local areas of the 11 phantoms: 5 HIFU spots, intensity 8.2 kW/cm², exposure 500 ms. Results are shown in Table 3. The phenomenon of heat accumulation in the focal zone can be explained by changes in the value and rate of heat transfer during mechanical shifts of phantom structures and the formation of conditions limiting the thermal conductivity of the studied environment.

Table 3

Temperature increase in the focal zone with 5 HIFU spots at an intensity of 8.2 kW/cm² and an exposure of 500 ms. (n=11)

№	Number of spots	Temperature in the focal zone
1	1	64,3±0,3*
2	2	83,2±0,4*
3	3	98,8±0,6*
4	4	103,0±1,2*
5	5	>103

Comment: * - statistically significant differences ($p < 0.01$).

Consequently, a feature of these HIFU modes on the PAG-3 polyacrylamide hydrogel phantom was a significant local temperature increase in the focal zone and a negligible temperature gradient in the outlying zones. It is likely that mechanical microcurrents form the conditions limiting the propagation of the thermal field. On the one hand, local thermodestruction occurs during HIFU exposure, and on the other hand, mechanical shifts form conditions limiting thermal field propagation, which is comparable with the features of thermal pattern formation in biotissues.

Of particular interest is the temperature gradient during multiple HIFU shots, but at different exposures. The dynamics of temperature gradient change depending on the number of HIFU spots with the intensity of 8.2 kW/cm^2 with exposures of 300 ms and 500 ms were evaluated. The data obtained are presented in Table 4,5.

Table 4

The dynamics of temperature changes in different zones of the phantom with an increase in the number of HIFU spots of exposure with an exposure of 300 ms

<i>№</i>	<i>Number of spots</i>	<i>The internal temperature of the phantom according to the readings of the 1st thermal sensor located at a distance of up to 1 mm from the thermal ablation zone</i>	<i>The internal temperature of the phantom according to the readings of the 2nd thermal sensor located at a distance of 5-10 mm from the thermal ablation zone</i>	<i>The internal temperature of the phantom according to the readings of the 3rd thermal sensor located at a distance of 15-25 mm from the thermal ablation zone</i>	<i>The internal temperature of the phantom according to the readings of the 4th thermal sensor located at a distance of 30-45 mm from the thermal ablation zone</i>
1.	5	73,1±0,3*	33,1±0,1*	23,7±0,1*	21,6±0,12
2	8	78,5±0,4*	34,1±0,08*	23,8±0,2*	21,8±0,1

Note: * - statistically significant differences ($p < 0.01$)

Table 5

The dynamics of temperature change in different zones of the phantom with an increase in the number of HIFU shots with an exposure of 500 ms

<i>№</i>	<i>Number of spots</i>	<i>The internal temperature of the phantom according to the readings of the 1st thermal sensor located at a distance of up to 1 mm from the thermal ablation zone</i>	<i>The internal temperature of the phantom according to the readings of the 2nd thermal sensor located at a distance of 5-10 mm from the thermal ablation zone</i>	<i>The internal temperature of the phantom according to the readings of the 3rd thermal sensor located at a distance of 15-25 mm from the thermal ablation zone</i>	<i>The internal temperature of the phantom according to the readings of the 4th thermal sensor located at a distance of 30-45 mm from the thermal ablation zone</i>
1.	5	88,5±0,3*	35,4±0,3*	24,0±0,07**	22,7±0,1
2	10	93,5±0,3*	37,6±0,2*	24,1±0,1**	22,8±0,21

Note: * - statistically significant differences ($p < 0.01$); ** - statistically significant differences ($p < 0.05$)

Thus, using the tissue-equivalent phantom PAG-3, the phenomenon of accumulation of thermal energy is observed in the affected area of the limited heat flow. This can be seen with single and multiple HIFU-induced exposures. Such features of the formation of the PAG-3 heat pattern bring it closer in its main characteristics to biological tissue structures.

There are some differences in the architectonics of thermal ablation zones in polyacrylamide hydrogel at different exposures with visual (Fig. 4-5) and ultrasonic (Fig. 6) control.

Figure 4. The section of thermal ablation in the form of a "saucer" on the surface of a PAG-3 phantom at a radiation intensity of 8.2 kW/cm^2 averaged overfocus up to 0.6 mm and an exposure of 300 ms .

The section of thermal ablation with a double shot of HIFU with an intensity of 23.3 kW/cm^2 and an exposure time of 600 ms , a feature of which was the presence of two "hourglass" spots.

Figure 5. Thermal ablation section in the form of a PAG-3 cone with a radiation intensity of 8.2 kW/cm^2 averaged overfocus to 0.6 mm and an exposure of 500 ms .

Cone-shaped zone of thermal ablation at 23.3 kW/cm^2 with a single shot lasting 800 ms with two areas of destruction of the phantom material according to the "cone" type.

Figure 6. Ultrasound image of the thermoablation zone in the form of a cone in a phantom (PAG-3) at a radiation intensity of 8.2 kW/cm^2 averaged overfocus up to 0.6 mm and an exposure of 500 ms .

Ultrasonic picture of the thermoablation zone (round shape) of the phantom (PAG-3) at a radiation intensity of 8.2 kW/cm^2 averaged overfocus up to 0.6 mm and an exposure of 1000 ms .

Discussion. The energy of the ultrasonic wave that propagates in biological tissues is partially converted into heat and partially transferred to the mass of the substance in the form of mechanical impulses that generate shear stresses and vortex microflows. The speed gradients reach $10^5 - 10^6 \text{ s}^{-1}$ and this is enough to "break" the cell membranes. At an ultrasound intensity of more than 0.1 W/cm^2 , along with mechanical effects, thermal energy begins to play a role. If destructive changes in tissues caused by an increase in temperature to 70°C and more are considered the result of the therapeutic effect of HIFU, then a number of questions remain completely unresolved. One of them is the distribution of the HIFU-induced heat pattern, which forms spatially inhomogeneous temperature zones that can integrate, thereby increasing the zone of thermal ablation, including healthy tissues.

A similar phenomenon in heterogeneous biological structures with heterogeneous hemodynamics is largely associated with nonlinear thermal effects that can generate zones with a small temperature difference, which limit the area of thermal damage. In this case, the total and distributed area of temperature patterns largely depends on the conditions of heat removal from the irradiated area, which ultimately determines the parameters of the thermal ablation zone and perifocal areas. The mechanical component is practically not taken into account when high-intensity focused ultrasound is applied to anisotropic biological tissues, which is associated with the generation of shock waves in the focal zone, which cause shear stresses in tissues and form hydrodynamic flows in a viscous medium.

Therefore, it is advisable to use the concept of the combined effect of HIFU in the focus area, when the focused acoustic wave front provides a local increase in temperature and initiates the formation of hydrodynamic flows. Most of the cavitation effects are directly related to the accumulation of energy in a very small volume of the medium. And in this case we are talking about the ratio of the energy density in the cavitation bubble to the energy density of the acoustic field. The high energy density in the cavitation bubble is largely determined by the very small volume of the substance at the moment the bubble reaches its minimum radius. It is believed that the radius of the bubble during ultrasonic cavitation at the end of compression $R_{\min}$ has a size in the range of 10^{-10} m with an equilibrium radius $R_0 = 10^{-6}$. And a change in the volume of the bubble by a factor of thousands causes the concentration of energy. The amount of stored energy can be expressed as $W = \Delta V \cdot P_0$, where ΔV is the change in volume as the bubble radius decreases from $R_{\max}$ to $R_{\min}$, and P_0 is the pressure in the environment. Assuming that $R_{\max} \gg R_{\min}$, we obtain the expression for the energy estimate [4]

$$W = 3 \cdot 4 \pi R_{\max}^3 \cdot P_0.$$

It should be assumed that the energy of an acoustic wave of high-intensity focused ultrasound increases the energy of the medium due to the kinetic energy of the vibrational motion of its elements that generate a thermal field, and potential energy associated with structural deformation of biological tissues. And the effect of energy cumulation in a cavitation bubble is associated with the transformation of the acoustic field energy into kinetic energy, part of which is transformed into thermal energy, and part is realized through cavitation effects, shear stress, and flows. But the thermodynamic parameters of the medium at the moment of bubble collapse can reach extremely high values, because the temperature in the bubble can differ by several orders of magnitude from the average temperature in the thermoablation zone. It can be assumed that it is this phenomenon of temperature gradients that underlies the formation of a thermal field under the influence of HIFU.

Thus, the proposed mechanism simulates the mechano-thermal effects of high-intensity focused ultrasound, which allows for dose planning of therapeutic exposure, which significantly minimizes the risk of damage to healthy structures.

Conclusion: the proposed model of dose planning of HIFU-induced exposure makes it possible to structure the architectonics of the distribution of thermal fields and shear stresses caused by cavitation effects. Personalization of the modes of exposure to ultrasound will provide

dosimetric control during direct therapy and minimize the risk of damaging effects of focused high-intensity ultrasound.

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