EFFECTS OF COLLAPSING CAVITATION ON HIFU-EXPOSED BIOLOGICAL OBJECTS

Annotation. Therapeutic significance in the studies of HIFU-induced effects of is attached to the local heating of tissues, but the role of the mechanical component caused by non-stationary cavitation is practically not taken into account. Calculations show that the temperature inside cavitation bubbles can differ significantly from the temperature in the thermal ablation zone, and the developing temperature gradient can change the formation of the thermal field. Collapsing bubbles can cause mechanical destruction of tissues.

Key words: acoustic field, energy density, temperature, thermal field, ultrasound, destruction, thermal ablation.

The use of focused high-intensity ultrasound (HIFU) is one of the promising methods of oncological diseases therapy, the main therapeutic effect of which is associated with local thermal destruction of deeply located pathologically altered tissues. Tissue’s local heating can significantly exceed the thermal threshold of protein denaturation (57–60 °C) and reach more than 100 °C, which leads to the explosive localized boiling or collapsing (unsteady) cavitation. When this happens, a significant part of energy is released, and it is capable of causing mechanical destruction of tissues with the cavitation effect implementation, which determined the purpose of this work.

Material and methods. To assess the mechanical component significance with a single HIFU exposure, we used 12 tissue-equivalent phantoms, they were created according to the method of A.I. Nevorotin (in modification of O.V. Plotkina) [1,2], a vascular-tissue model, for which the tongues of 7 grass frogs (Rana Temporaria) were required. Before the start of the experiment, the frogs were anesthetized (10% Urethane solution in a volume of 0.4 ml / 100 g) with the solution injected into their dorsal lymph sac. The frogs were placed on a plate with a “window” for transmitted light, over which the frog’s tongue was carefully straightened and fixed. The choice of the model was associated with the availability for real-time imaging, small dimensions, which made it possible to evaluate the temporal effects of anisotropic biological tissue deformation by an acoustic wave.

The experimental work was carried out on a stand which included an ultrasound diagnostic module based on the Angiodin-1 scanner (“Bioss”, Russia) and an installation consisting of an emitter generating high-intensity ultrasound and a mobile “Diater” module for HIFU therapy. A concave transducer H-148 S / N 010 (Sonic Concepts, Inc.) with a central oscillation frequency of 2.5 MHz (minimum frequency of 1.4 MHz), an active diameter of 64 mm and a central hole of 20 mm was used to focus the radiation.

To ensure the passage of ultrasonic waves, we used a conducting medium – still (degassed) water. For real-time visualization of changes in blood flow in the microhemocirculation bed of the frog’s tongue, a video setup with a microscope (Wild M420, Switzerland) with a lens (Makrozoom) with a magnification of 63 × and a digital camera (Basler, Germany).

The research results were processed using the IBM SPSS Statistics 21 software package.

Results. Initially the intensity of focused ultrasonic single exposure was 8.2 kW / cm2 with exposure duration varying from 300 ms to 1000 ms. Immediately after a single HIFU exposure, tissue-equivalent phantoms were carefully removed from a container filled with still water and we measured the diameter of the surface defect on the biophantoms surface in the thermal ablation zone; the obtained results of the analysis of the biophantoms state made it possible to reveal a number of specific features:

1) after a single exposure to HIFU with an intensity of 8.2 kW / cm2, crater-shaped (cone-shaped), rounded “funnels” with smooth contours were formed on the biophantoms surface in the thermal ablation zone;

2) the diameter of the cone-shaped funnel in the tissue-equivalent phantom depended on the HIFU time exposure with an intensity of 8.2 kW / cm2 (Fig. 1);
3) Immediately after a single exposure to a focused high-intensity ultrasound, "floating" homogeneous echo structures of small size, caused by the ejection of the phantom material, were located in degassed water. Their genesis is largely associated with the effect of explosive collapsing cavitation (Fig. 2).

4) The thermal ablation zone during an ultrasound scanning of a phantom in all cases was shaped in the form of a cone (Fig. 2), the dimensions of which varied depending on the exposure.

Thus, the nature of the changes during a single exposure to focused high-intensity ultrasound testified not only to the role of the thermal component as a leading factor of exposure, but also to the mechanical component induced by cavitation effects in a viscous medium of a tissue-equivalent phantom. To assess the role of the mechanical component in the tissues of a living organism, the reaction of the microhemocirculatory bed of the frog's tongue was studied and evaluated. After recording the initial blood flow aquagel was applied to the frog's tongue and a single HIFU treatment was carried out with an intensity of 8.2 kW cm², duration of 300 and 500 ms. Biomicroscopy of the frog tongue vessels with video recording of blood flow was performed immediately after the completion of irradiation. The process of
moving the anesthetized animal from the HIFU generator to the biomicroscopy unit took about 1 minute. Changes in the diameter of the vessels were analyzed using the video recordings of the blood flow.

It was found that immediately after a single exposure to HIFU exposure with an exposure of 300 ms on the surface of the tongue, 3 frogs revealed a clear zone of direct rounded damage, in the form of hemorrhage, with an uneven optical density with an area of about 10-14 mm² (Fig. 3). The vessels in the area of direct injury were not detected; above the surface of this area, individual vessels were visible, in which blood flow was preserved. In the tissues of the tongue adjacent to the destruction zone, blood flow was partially or completely preserved, but the number of functioning capillaries was reduced. The diameter of arterioles in the affected area decreased by 27%; the diameter of the venules decreased by 7.5%.

Figure 3. Zone of direct injury after a single HIFU exposure.

In all cases, with an increase in exposure to 500 ms, total tissue destruction was demonstrated up to its rupture in the thermoablation zone. This indicated the importance of the role of the cavitation effect during HIFU exposure.

Figure 4. Zone of total destruction with rupture of tongue tissues in 3 frogs after a single HIFU-induced exposure with an exposure of 500 ms.

**Discussion.** In recent years, the attention of specialists has been focused not only on the thermal, but also on the mechanical component of the impact of high-intensity focused ultrasound on anisotropic biological tissues. The cavitation effect of ultrasound is associated both with the generation of shock waves in the focal zone causing shear stresses in the tissues and forming hydrodynamic flows in a viscous medium, and with a thermal effect, leading to a change in gas saturation and temperature of the medium. Therefore, it is advisable to assume about the combined effect of HIFU in the focal zone: when the focused acoustic wave front provides a local increase of 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.

In this case, it can be said 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 determined by the very small volume of the substance at the moment when the bubble reaches its minimum radius.

It is believed that the radius of the bubble during ultrasonic cavitation at the end of compression $R_{\text{com}}$ has a size in the range of $10^{-10}$ m with an equilibrium radius $R_0 = 10^{-6}$. A change in the volume of the bubble thousands of times causes the concentration of energy. At the same time, 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:

$$W = \Delta V \cdot P_0,$$

where $\Delta V$ - is the change in volume as the bubble radius decreases from $R_{\text{max}}$ to $R_{\text{min}}$, and $P_0$ - is the pressure in the environment.

Assuming that $R_{\text{max}} >> R_{\text{min}}$, - the expression for estimating the energy has been obtained.

$$W = 3\sqrt[4]{4 \pi R_{\text{max}}^3} \cdot P_0.$$

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, as well as potential energy associated with structural deformation of biological tissues. The effect of energy cumulation in a cavitation bubble is probably 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 stresses, and flows.

However, 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, giving it an oval shape (Fig. 5).

**Figure 5. Thermal image of the shape of the heat spot after HIFU-induced exposure**
*(the numbers indicate the temperature in °C).*

**Conclusion.** Thus, the thermodynamic parameters of the medium at the moment of bubble collapse when exposed to focused high-intensity ultrasound reach extremely high values, which leads to mechanical ruptures in biological tissues and the formation of defects in tissue-equivalent phantoms. Despite the extensive experimental material available, a fully adequate model of the processes associated with the pulsation of a cavitation bubble in an inhomogeneous medium has not yet been developed. The difficulties are largely associated with a wide range of changes in bubble volume, density, temperature, as well as extremely short time intervals.

**References**
