EXPERIMENTAL BIOLOGY

Assessing the Safety of Focused Ultrasound for Noninvasive Exposure of the Heart

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Measurements of temperature and macroscopic and microscopic studies show a relatively normal status of the presenting tissue at the site of focused ultrasonic beam during noninvasive exposure of the heart through the thoracic wall in dogs: the temperature in the subcutaneous fat of the thoracic wall partially submerged in water is no higher than 38°C and 40.5°C in the periosteum. Warming of the periosteum during treatment by noninvasive methods may be the limiting factor at sites where the bones are located close to the surface, for example, the ribs. Skin burns may be prevented by focused ultrasonic exposure through aqueous medium.

Key Words: *focused ultrasound; noninvasive exposure; microthermocouple*

Focused ultrasound (FUS) is used in medicine and biology for noninvasive local exposure of organ and tissue structures [1,7]. However, we failed to find any reports about biological effects of high-frequency US oscillations on the heart during noninvasive local exposure.

The safety of US exposure for the adjacent tissues is an important condition for practical exposure of deep structures of tissues and organs to FUS. One important factor is an increase in the temperature of tissues at the site of a convergent US beam due to absorption of US energy. The contribution of absorption to complete extinguishing of US energy varies from 30 to 70% [3]. Other causes of changes in the temperature of tissues exposed to US (periodical changes resulting from oscillations of the medium, heating by gas bubbles in the tissue, thermal changes caused by cavitation, etc.) are negligible in comparison with heating resulting from US absorption.

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MATERIALS AND METHODS

Contact-free methods for measuring the temperature of biological tissues: acoustothermography, acoustothermometry, and radiothermometry have been recently developed [4]. However, there are no commercial devices permitting noninvasive measurements of local changes in the temperature of deep-lying tissues and organs.

In order to assess tissue injuries along the US beam and the heating of the chest bones during US exposure of the heart we measured temperature at several sites located at different distances from the surface of US device to the focus of exposure. The temperature was measured with a special device consisting of microthermocouples, direct current amplifier, and a recorder (V7-35 digital voltmeter).

The temperature was measured both *in vitro* and *in vivo* in order to compare the transformations of temperature in biological tissue under the effect of US under different conditions.

Manganin-constantan thermocouples with the diameter of thermojunction no more than 0.2 mm

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were placed in an injection needle and hermetically sealed. The sensitivity of thermojunction at temperatures 15-55°C is about 100 mV/°C and their characteristics are linear.

The required intensity of US in the focal area of the device was set up by regulating the output power of the generator using calibration curves plotted during radiometry of US intensity in the focal area [2].

The dogs were premedicated with 0.25% droperidol in a dose of 0.15 ml/kg intramuscularly and with sodium thiopental in a dose of 1.0 ml.

The dogs were fixed in special devices lying on the left side. At this posture the heart adheres closer to the chest and a larger "acoustic window" is formed through which the exposure is carried out.

In 11 experiments, the temperature was measured *in vivo* in 3 sites at a different depth along the arbitrary acoustic axis of US radiation: on the surface of the skin, in the periosteum, and in soft tissues on the internal surface of the chest.

The generator operated in the pulse mode with the exposure pulse triggered synchronously with the *QRS* complex of the ECG. The duration of exposure and, consequently, the time during which temperature was increasing in the anterior thoracic wall in the US field was 20 min. The duration of pulse t_p was 0.1 sec, US intensity in the focal area of the device I_F=1000 W/cm², exposure frequency f=1 MHz. The total duration of US exposure at a heart rate of 100 beats/min (1.7 Hz) and t_p=0.1 sec was Σt_p=20×100×0.1=200 sec.

Needle thermocouples were inserted in the above-mentioned sites after shaving. After preliminary echolocation, the arbitrary acoustic axis of the generator was oriented to the apex of the heart, which coincided in the majority of cases with the apical impulse, the generator was applied to the skin, and US exposure was realized through acoustic gel or water, with monitoring temperature changes and following up the course of exposure by ECG.

In 5 cases, US exposure was carried out by directly applying the generator to the skin through a layer of acoustic gel, in 6 cases the anterior thoracic wall of the dog was submerged in 18°C distilled water, with the generator fixed to the skin with a special device.

The center of the focal area was located at a depth of 52 mm from the skin surface, the intensity of US on the skin surface (with consideration for the concentration coefficient for the generator used) I=5 W/cm² (at I_F=1000 W/cm²). This value is no higher than the permissible intensity used in physiotherapy [4]. The exposure parameters were chosen based on the results of experiments on the open chest [3].

The morphology of the anterior thoracic tissue preparations exposed to US was studied macroscopically and microscopically. At the end of the experiment tissue specimens were fixed in neutral formalin. Tissue sections were stained with hematoxylin and eosin, and by the methods of Van Gieson, Heidenhain, and Lillie. The preparations were examined under a light microscope.

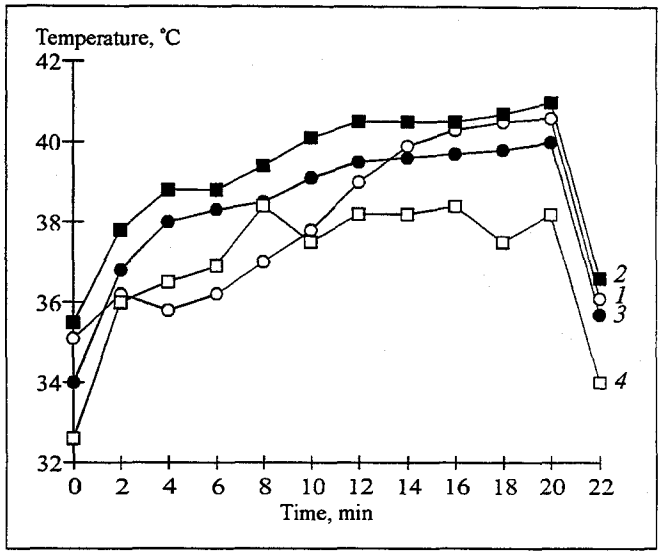

Fig. 1. Measurements of temperature in the anterior thoracic wall of a dog during ultrasonic exposure *in vivo*. I_F=1000 W/cm², f=MHz, t_p=0.1 sec. Subcutaneous fat through gel (*1*) and water (*4*); *2*) periosteum; *3*) muscle tissue.

RESULTS

Figure 1 illustrates changes in the *in vivo* temperature of subcutaneous fat, periosteum, and muscle tissue. Comparison of the *in vitro* and *in vivo* diagrams showed that:

- *in vivo* there is a tendency toward a monotonous accelerated increase in the periosteum and skin temperature, but changes in the temperature are less pronounced than *in vitro,* probably due to the bloodflow effects;
- the temperature in the subcutaneous fat of an animal partially submerged in water is no higher than 38°C after a 20-min US exposure, whereas during US exposure through gel the temperature at the same site is 41°C;
- in the periosteum, the temperature is 40.5°C by the 10th min of US exposure and is virtually the same till the end of the session;
- the rate of the temperature growth after the generator is switched on and the rate of temperature decrease after it is switched off is the same for all tissues.

Macroscopic examinations of preparations of the dog thoracic wall (3 samples per zone), collected 6 days after US exposure through gel according to the

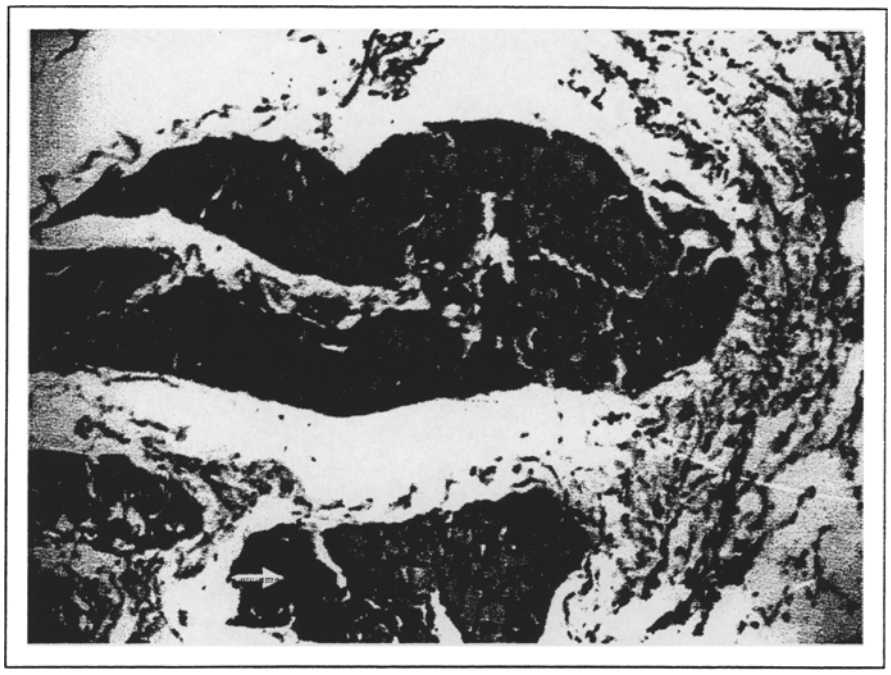

Fig. 2. Regenerative inflammation of the subcutaneous fat in the anterior thoracic wall of a dog at the zone of focused ultrasonic beam (shown with an arrow). I_F=1000 W/cm^2, f=1 MHz, t_p=120 sec, follow-up for 6 days, hematoxylin and eosin staining, ×80.

above schedules, generally revealed a white 3×4 cm spot on the lateral surface of the pericardium. There were no liquid or adhesions in the pericardial cavity. Another whitish spot 3×3 cm formed on the anterolateral surface of the right ventricle, the myocardium was compact. The pericardial section was as thick as 0.5-1 mm, the endocardium being without changes. Compact white-gray sites were found in the subcutaneous fat exposed through gel, and the rib was porous at the same sites if dissected. After exposure through water, no macroscopic changes of this kind were seen at the same sites of the thoracic wall.

Microscopic examination revealed partial "melting" of damaged subcutaneous fat along the US ray in the pericardium 6 days postirradiation (3 acute experiments, exposure through water). The lumen was intact even in the smallest arteries. Zones of cellulitis were discernible along the ray in the chest (Fig. 2), i. e., the processes were similar to those seen in the pericardium. Local inflammation in response to potent US exposure was observed in some muscle bundles in the same zone. Hard tissues (bones and cartilages) retained their structure, and the periosteum remained intact.

Measurements of temperature and macroscopic and microscopic examinations showed that the above scheme of US exposure is sufficiently safe for the tissues adjacent to the zone of the convergent US beam.

An accelerated increase in the periosteum temperature in the US field may be due to selective heating of the interface between tissues with different acoustic properties. From our results it can be concluded that warming of the periosteum is a limiting factor in noninvasive therapy at sites where the bones are located close to the body surface, for example, chest ribs. Skin burns may be prevented by performing FUS through aqueous medium.

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