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Selection of Exposure Parameters for a HIFU Ablation System Using an Array of Thermocouples and Numerical Simulations

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Image-guided High Intensity Focused Ultrasound (HIFU) technique is dynamically developing technology for treating solid tumors due to its non-invasive nature. Before a HIFU ablation system is ready for use, the exposure parameters of the HIFU beam capable of destroying the treated tissue without damaging the surrounding tissues should be selected to ensure the safety of therapy. The purpose of this work was to select the threshold acoustic power as well as the step and rate of movement of the HIFU beam, generated by a transducer intended to be used in the HIFU ablation system being developed, by using an array of thermocouples and numerical simulations. For experiments a bowl-shaped 64-mm, 1.05 MHz HIFU transducer with a 62.6 mm focal length (f-number 0.98) generated pulsed waves propagating in two-layer media: water/*ex vivo* pork loin tissue (50 mm/40 mm) was used. To determine a threshold power of the HIFU beam capable of creating the necrotic lesion in a small volume within the tested tissue during less than 3 s each tissue sample was sonicated by multiple parallel HIFU beams of different acoustic power focused at a depth of 12.6 mm below the tissue surface. Location of the maximum heating as well as the relaxation time of the tested tissue were determined from temperature variations recorded during and after sonication by five thermo-couples placed along the acoustic axis of each HIFU beam as well as from numerical simulations. The obtained results enabled to assess the location of each necrotic lesion as well as to determine the step and rate of the HIFU beam movement. The location and extent of the necrotic lesions created was verified using ultrasound images of tissue after sonication and visual inspection after cutting the samples. The threshold acoustic power of the HIFU beam capable of creating the local necrotic lesion in the tested tissue within 3 s without damaging of surrounding tissues was found to be 24 W, and the pause between sonications was found to be more than 40 s.

Keywords: automated HIFU ablation system; threshold acoustic power of HIFU beam; *ex vivo* tissue; necrotic lesion; thermocouple array.

1. Introduction

Image-guided High Intensity Focused Ultrasound (HIFU) technique is promising and dynamically developing thermal technology for treating solid tumors due to its non-invasive (non-surgical) nature (ter Haar, 2016; Zhou, 2011). The physical principles of this technique, used in thermo-ablative therapy of tumors, are known and rely on rapid (< 3 s) heating of a small volume inside the treated tissue to a temperature above 56°C leading to immediate cell death (ter Haar, 2007). To heat up the entire tumor volume, a mechanical or electronic movement of the focus of the HIFU beam under the imaging control (Hynynen, Jones, 2016) is applied. This technique is capable of destroying solid tumors with sizes from a few mm to several cm via thermal and cavitational mechanisms without damaging tissues surrounding the tumor (Fry *et al.*, 1955).

To guide the HIFU ablation the magnetic resonance imaging (MRI) or ultrasound imaging (USI) are used. Existing MRI-guided HIFU ablation systems and their operating costs are very high and the duration of treatment is much longer than that using ultrasound imaging guidance (Orsi *et al.*, 2010). Our intension was to develop, design and build an ultrasound imaging-

guided HIFU ablation system for treating solid tumors in small animals. The design of the proposed device, including the HIFU ablation system, ultrasound imaging-guided targeting system and HIFU beam positioning control system, is described in (Kujawska *et al.*, 2017).

Before the device was built, a series of experimental studies had been needed to determine the threshold acoustic power of the HIFU beam capable of creating coagulation necrosis in the tested tissue in less than 3 s and to assess the tissue relaxation time determining the rate of the HIFU beam movement in order to minimize treatment time.

The results of these studies were necessary to assess the feasibility and efficiency of application of the HIFU transducer intended to be used in the HIFU ablation system being developed for preclinical studies on treatment of solid tumors in small animals as well as for determination of characteristics of thermal lesions formed in the tested tissue.

2. Materials and methods

2.1. HIFU ablation probe

For experiments a bowl-shaped H-101 transducer (Sonic Concepts Inc, Bothell, WA, USA) with an effective diameter of 64 mm, focal length of 62.6 mm (f-number 0.98) and resonance frequency of 1.05 MHz was used. The transducer had a standard 50 Ω matching circuit and was excited by sinusoidal pulses with selected voltage, duration and duty-factor. The beam patterns produced by this transducer in water were measured by a needle hydrophone. An example of the simulated numerically and measured axial and radial (in the focal plane) pressure distributions in the HIFU beam with an acoustic power of 8 W generated by this transducer in water is shown in Fig. 1. An average acoustic power of the pulsed HIFU beams used was estimated (with an uncertainty of 5%) from radiation

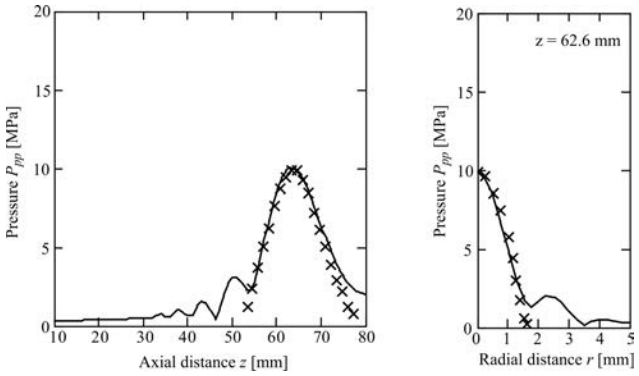

Fig. 1. Axial (left) and radial (right) peak-peak pressure distributions calculated (solid lines) and measured (points) for the HIFU beam with an acoustic power of 8 W generated by the transducer used and propagating in water.

force measurements using an ultrasound power meter. The HIFU beams with varied acoustic power propagated in two-layer media: water/*ex vivo* pork loin were studied. The thickness of the water layer was determined from the nonlinear propagation model (Wójcik *et al.*, 2006) and amounted to 50 mm for the transducer used.

To determine a threshold power of the HIFU beam capable of inducing in the tested tissue a local temperature rise above 56°C during less than 3 s the HIFU beams with an acoustic power varied from 8 W to 36 W were studied. Each beam was focused at a depth of 12.6 mm below the tissue surface. The *in situ* intensity, i.e. the intensity I_{SA} induced within the tested tissue by each HIFU beam at the site of its activity (spatially averaged over the half-power cross-section of the beam in the focal plane) was determined from numerical simulations of spatial pressure distributions in the pulsed HIFU beams propagating in the two-layer media: water/tissue (50 mm/40 mm) using our nonlinear propagation model (Wójcik *et al.*, 2006) that required the following tissue parameters which values were taken from literature: the pork loin density ρ_0 = 1060 kg/m^3 (Duck, 1990), sound velocity c = 1620 m/s (Koch *et al.*, 2011), attenuation coefficient $\alpha = 11 \cdot 10^{-6}$ Np/(m·Hz^b) (Koch *et al.*, 2011), power index of attenuation dependence on frequency b = 1 (Nassiri *et al.*, 1979), nonlinearity parameter B/A = 8 (Law *et al.*, 1985) and thermal conductivity coefficient K_t = 0.52 W/(m·°C) (Kujawska *et al.*, 2014).

For the HIFU beams with increasing sound power equal to 8 W, 16 W, 20 W, 24 W, 28 W, 32 W, and 36 W the estimated *in situ* intensity I_{SA} was determined to be equal to 134 W/cm^2, 277 W/cm^2, 364 W/cm^2, 461 W/cm^2, 571 W/cm^2, 679 W/cm^2, 797 W/cm^2, respectively. The calculated volume of the −6 dB ellipsoidal focal region for each HIFU beam used, with the same duration and duty-factor, was approximately the same regardless of its acoustic power/intensity. The axial length of the focal zone was found to be about 12 mm and diameter about 1.8 mm.

2.2. Experimental setup

The block diagram of the experimental setup is shown in Fig. 2, the photo of the water tank with the tissue chamber and thermocouples is shown in Fig. 3. All measurements were carried out at tissue temperature of 36°C.

As shown in Fig. 2, an electronic transmission system comprising an Agilent 33250A function generator (Colorado Springs, USA) and an ENI 3100LA power amplifier (55 dB) (Rochester, New York, USA) was used to excite the HIFU transducer with electric sinusoidal pulses of the selected amplitude, duration and repetition period. The output of the amplifier excited

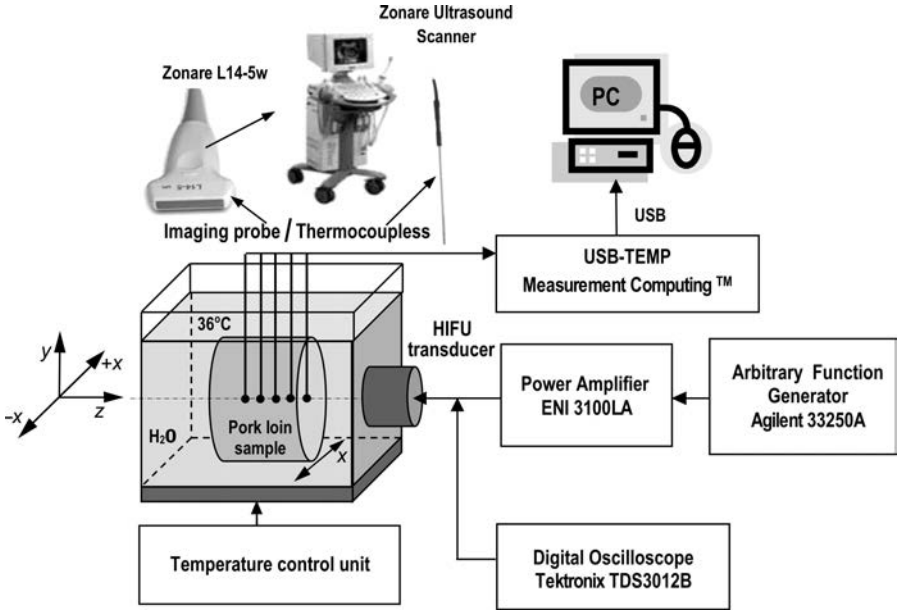

Fig. 2. Schematic diagram of the experimental setup for creating necrotic lesions within an *ex vivo* tissue sample by HIFU beams, for measuring temperature rises induced along the HIFU beam axis and for ultrasound imaging of formed lesions.

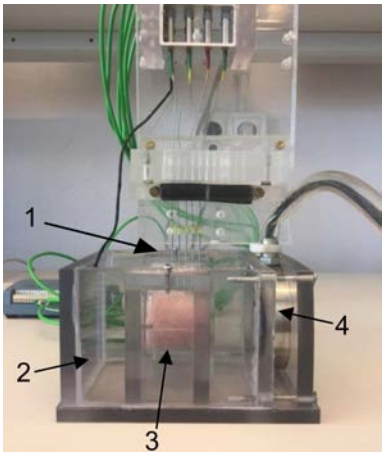

Fig. 3. A photo of a HIFU system for measuring temperature rises induced in tissue by the HIFU beam used: 1 – array of thermocouples, 2 – water tank, 3 – tissue chamber, 4 – HIFU transducer.

the transducer to produce the HIFU beam with a selected acoustic power. To generate the HIFU beam with an average acoustic power varied from 8 W to 36 W, the voltage applied to the transducer was varied from 131 V_{pp} to 371 V_{pp}.

The acoustic power for each beam used was measured using an UPMDT1E ultrasound power meter (Ohmic Instruments, St. Charles, MO, USA). The HIFU transducer was mounted rigidly in a side wall of a tank filled with a distilled water with a temperature controlled by a custom electric heater. The waveform of tone bursts generated by the transducer was recorded using a TDS3012B digital oscilloscope (Tektronix, Beaverton, USA).

2.3. Preparation of tissue samples

When the effect of a single sonication parameter on the location and extent of the necrotic lesion was studied, the tissue samples were prepared from the same piece of pork loin. The tissue samples were cut with a cylindrical knife into blocks, then degassed and inserted into a cylindrical polycarbonate chamber with an internal diameter of 43.5 mm and height of 40 mm. To prevent the water/tissue surface from folding, the chamber had sound-transparent windows made of 20-μm thick Mylar film, stretched tightly at each end using two holders. Then, the tissue chamber was immersed in a water tank with a controlled 36°C temperature. The construction of the water tank provided a coaxial position of the tissue chamber with the HIFU transducer and the axial distance between them determined from the non-linear propagation model. As was mentioned above for the transducer used this distance amounted to 50 mm. Then the targeted HIFU beam focus was inside the tissue at a depth of 12.6 mm below the tissue surface. Before each sonication the temperature inside the tissue sample was controlled by thermocouples placed inside the tissue along the acoustic axis of the HIFU beam. During sonication the temperature rises induced in each sample were monitored using TP-201 needle thermocouples (Czaki Termo-Product, Raszyn, Poland). Multiple parallel necrotic lesions were created inside each sample by moving the tissue chamber horizontally left or right from the central HIFU beam axis by ±2 mm or by turning its back to the front between exposures. The effective exposure time (number of generated pulses) was controlled using a custom software. During the experiments, ultra-

sound pulses with a duration of 20 μs, 2 ms or 200 ms and a duty-factor of 0.2 were studied.

2.4. Temperature measurement protocol

As already mentioned above, measurements of temperature rises induced locally in the tested tissue by each HIFU beam with selected acoustic parameters were carried out using five 0.2-mm thermocouples placed in the tissue on the acoustic axis of the HIFU beam with a step of 5 mm starting from a depth of 5 mm below the tissue surface. The thermocouples, rigidly connected to each other, were located in the tissue through 0.5-mm hypodermic needles inserted through the holes in the 10-mm thick cover of the water tank ensuring their precise position on the HIFU beam axis. The uncertainty of positioning for each thermocouple was about ±0.5 mm. Due to a small diameter of the thermocouples their influence on measurement results was considered negligible. The temperature rise detected by each thermocouple was recorded in steps of 0.65 seconds by USB-TEMP unit (Measurement Computing, Norton, USA) and transferred to the PC memory. In order to process data obtained and to visualize the temperature-time plots a TracerDAQ (MicroDAQ.com Ltd, Contoocook, NH, USA) software was used. The maximum temperature rise determined the position of the maximum heating spot, which, in turn, determined the depth of location of the necrotic lesion center. The example of the temperature rises $\Delta T(t)$ induced in the tested tissue during its exposure to the HIFU beam, measured by thermocouples placed along the acoustic axis of this beam and averaged from measurements in three tissue samples is shown in Fig. 4.

The construction of the measuring setup allowed to minimize errors resulting from the refraction of the HIFU beam, the inaccuracy of its concentricity with the cylindrical tissue chamber and the inaccuracy of positioning the thermocouples.

2.5. Visualization of necrotic lesions

After sonication, the necrotic lesions induced within each tissue sample were visualized in both, the axial and focal planes using a Zonare ultrasound scanner (Zonare Medical Systems Inc., Mountain View, CA, USA) equipped with a Zonare L14-5w imaging probe. It was possible due to the narrow rectangular opening along the wall of the cylindrical tissue chamber and the sound-transparent windows at each its end. The location and extent of thermal lesions in the tissue, visible as hyper-echoic areas on the ultrasound images of axial and radial cross-sections of the tissue sample was identified and compared with the position of thermocouples.

Then, each tissue sample, placed in the cylindrical chamber, was cut along a plane including axes of all HIFU beams used, so that the thermal lesions induced by them was visible in their maximum length and width. Sizes of necrotic lesions and their location were measured manually using a caliper with an accuracy of ±0.1 mm as well as with an ImageJ software (Rasband, 1997–2006) using the scale of the photographed ruler. The deviation between the position of the center of the necrotic lesion and the position of thermocouple which recorded the maximum temperature rise was analyzed.

3. Results and discussion

In order to determine the threshold acoustic power of the HIFU beam, generated by the transducer intended to be used in the HIFU ablation system capable of inducing a necrotic lesion in a small volume within a treated tissue within 3 s without damaging adjacent tissues, the influence of the beam power on the temperature rises induced locally in the tested tissue during its exposure to focused ultrasound was estimated and quantitatively analyzed. The pulsed HIFU beams with a varied acoustic power (8–36 W) propagated in two-layer media water/*ex vivo* pork loin tissue (50 mm/40 mm) were studied theoretically and experimentally. Based on the obtained experimental results, it was shown that only beams with an acoustic power equal to or exceeding 24 W (I_{SA} = 461 W/cm^2) were able to lead to the local temperature rise above 56°C in less than 3 s. Exemplary, averaged for three samples, increases in temperature as a function of exposure time, measured by 5 thermocouples placed inside the tissue along the acoustic axis of the HIFU beam at depths of 5 mm, 10 mm, 15 mm, 20 mm, and 25 mm below the tissue surface are shown in Fig. 4.

As shown in this figure, the maximum rise in temperature was recorded by two thermocouples placed at a depth of 10 mm and 15 mm below the tissue surface. This indicates that the maximum energy of the HIFU beam was delivered to the intended focal zone (near the beam focus at a 62.6 mm, that is, at a depth of 12.6 mm below the tissue surface). This figure also shows that the relaxation time required to return the tissue temperature to its original level was above 40 seconds.

An example of the result of numerical predictions of the thermal field induced locally within the tested tissue by the HIFU beam with the same 24 W acoustic power during 3 seconds of sonication is shown in Fig. 5 for the beam focal zone (xz plane). The temperature distributions were calculated in the MatLab environment using the v1.2 HIFU simulator software provided by the FDA (Soneson, 2011).

The obtained results for the calculated thermal fields were in good agreement (within ±5°C) with the measurement data. Differences between theoretical and experimental results could be due to the in-

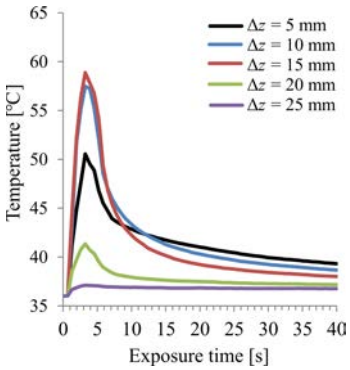

Fig. 4. Averaged for three tissue samples temperature rises induced in *ex vivo* pork loin tissue by the HIFU beam with an acoustic power of 24 W, pulse duration of 20 µs and duty-factor of 0.2. The maximum value of the standard deviation with increasing depth was ±5.5°C, ±5.6°C, ±7.3°C, ±2.5°C, ±0.7°C, respectively.

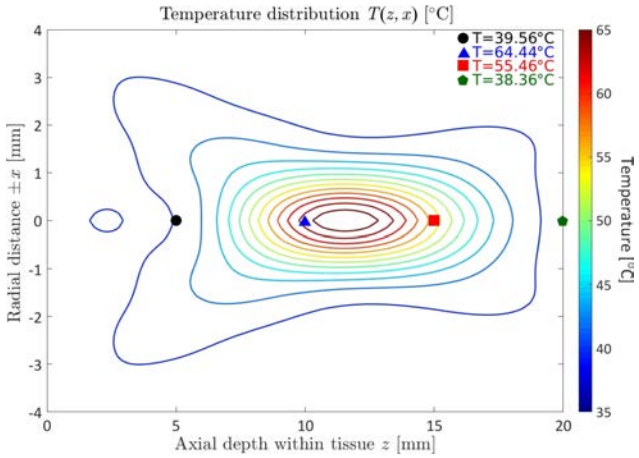

Fig. 5. Calculated temperature distribution, induced in the tested tissue by the HIFU beam with a 24 W acoustic power focused at the depth of 12.6 mm below the tissue surface during 3-second exposure. The symbols indicate the axial depth below the tissue surface at which the temperature was measured.

accuracy of the tissue thermal or acoustic parameters assumed in the model.

After each tissue sample was exposed to several (from 4 to 6) parallel beams, visualization of its axial and radial cross-sections was performed using an ultrasound imaging probe. The images obtained indicated that the visible hyper-echoic areas reflecting the necrotic lesions are located on the imaging plane in the intended area. Figures 6–8 show examples of ultrasound images of the examined tissue sample after its sonication by four (two exposures at the front and back) parallel HIFU beams of different acoustic power distant from each other by 4 mm.

After cutting each tissue sample along the axial plane, measurements of deviation of the center of each visible necrotic lesion from the intended targeted posi-

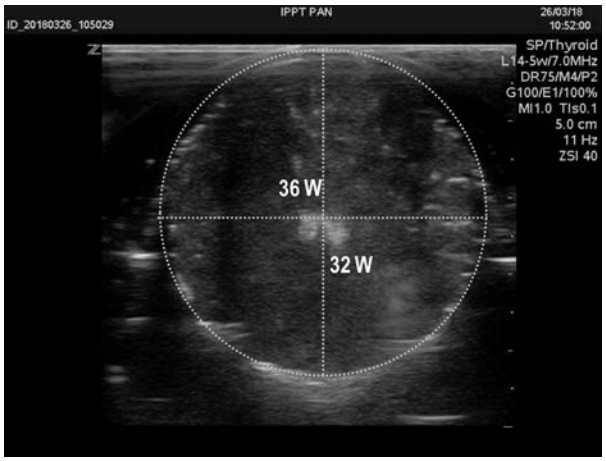

Fig. 6. Ultrasound image of the radial section (xy) of the tested tissue sample placed in the cylindrical chamber after its exposure to two parallel, spaced by 4 mm, HIFU beams with the acoustic power of 32 W and 36 W. The section at a focal plane of the beams is shown.

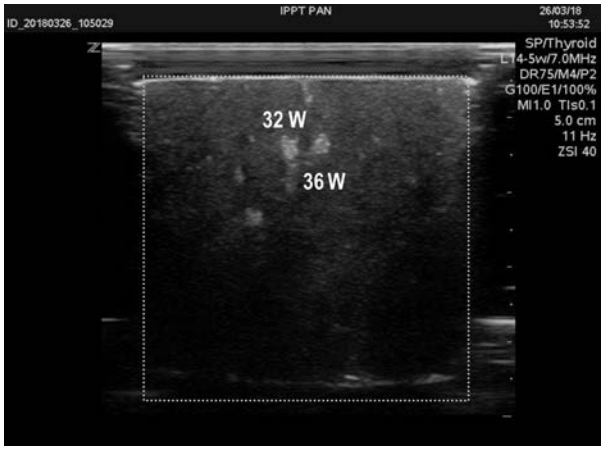

Fig. 7. Ultrasound image of the axial section (xz) of the tested tissue sample placed in the cylindrical chamber after its exposure to two parallel, spaced by 4 mm, HIFU beams with the acoustic power of 32 W and 36 W.

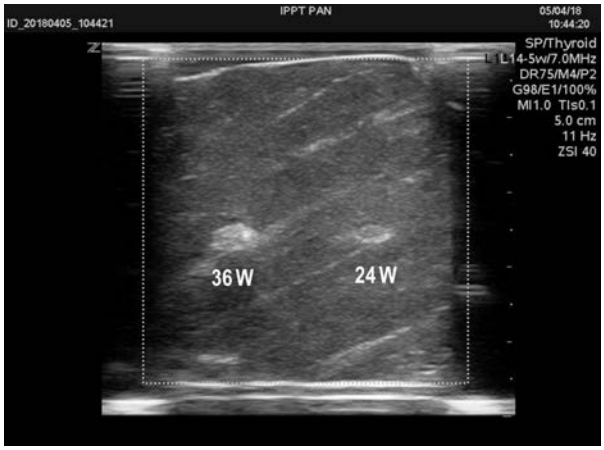

Fig. 8. Ultrasound image of the axial section (yz) of the tested tissue sample placed in the cylindrical chamber after its exposure at the front and back to two coaxial HIFU beams with the acoustic power of 24 W and 36 W.

tion were performed. The targeted position was located on the HIFU beam axis at a depth of 12.6 mm below the tissue surface. A photograph of exemplary necrotic lesions formed in the *ex vivo* pork loin sample after its exposure to four parallel HIFU beams with the same pulse duration, duty-factor and varied acoustic power is shown in Fig. 9.

As shown in this figure, the center of each necrotic lesion created by HIFU beams with the same pulse duration and duty-factor, and varied acoustic power lies at a depth of about 12.5 mm (with a deviation of ±1 mm), i.e. approximately at the planned targeted location.

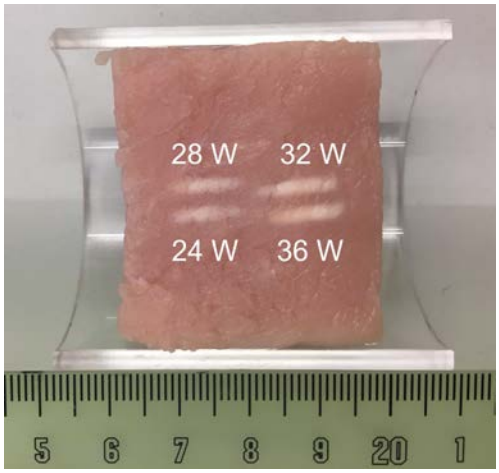

Fig. 9. Photo of axial section of the tissue sample sonicated at the front and back by two parallel HIFU beams with acoustic power varied between 24 W and 36 W.

The inaccuracy of targeting the HIFU beam focus used in these studies on the desired area within the tissue may have been due to, i.a. misalignment between the HIFU transducer and tissue chamber, inaccuracy of placing the thermocouples on the HIFU beam axis, inaccuracy in targeting the imaging plane and inaccuracy in the sectioning of the sample. To minimize these errors, the construction elements of the experimental setup were made with great precision and fulfilled the functional and structural assumptions.

4. Conclusions

Experimental results obtained showed that the HIFU beam generated by the transducer, intended to be used in the automated ultrasound imaging-guided HIFU ablation device being developed for treating solid tumors in small animals, is able to produce well-defined thermal lesions in the intended small volume within the *ex vivo* tissue examined without damaging the surrounding tissues. To assess the threshold acoustic power of the HIFU beam capable of creating local necrotic lesions inside the tested tissue during the exposure less than 3 seconds an array of thermocouples placed in the tissue along the HIFU beam axis was used. The feasibility and efficiency of necrosis formation in the tested tissue has been verified using ultrasound images of the axial and radial tissue cross-sections as well as using visual inspection after cutting the tissue samples. Quantitative analysis of the results obtained showed that the threshold acoustic power of the HIFU beam which can be used in our ultrasound imaging-guided automated HIFU ablation device amounted to 24 W (I_{SA} = 461 W/cm^2). Meanwhile, the minimum time interval between exposures resulting from the tissue relaxation time and determining the rate of the HIFU beam movement over the treated tissue volume was found to be 40 seconds. The maximum step between exposures was found to be about 1.8 mm.

Acknowledgment

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