Thresholds for Focal Ultrasonic Lesions in Rabbit Kidney, Liver, and Testicle

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Abstract—Thresholds are reported for production of focal ultrasonic lesions in rabbit liver, kidney, and testicle for 2 and 6 MHz, single pulse exposures ranging in length from 1 to 60 s. Intensity-exposure time thresholds are found to be nearly independent of frequency as shown in earlier work for brain tissue. The results compare favorably with a thermal model for prediction of thresholds which considers the activation energy for thermal destruction of the tissues, their thermal diffusivity, absorption coefficients, time and intensity of exposure, and baseline temperature. All thresholds are of the same magnitude as those previously reported for brain. Those differences which are observed can be explained by the thermal model for the action of ultrasound on tissue.

INTRODUCTION

The potential applications of focused ultrasound in neurological surgery have motivated studies by several investigators to determine thresholds for lesion production in brain tissues [1-3]. In addition to its obvious importance for surgical applications, this has given important information concerning the safety of medical applications of ultrasound, and has also contributed to an understanding of the mechanism of the action of ultrasound on tissue. At intensities less than 200 W/cm^2, it appears that tissue destruction can be explained on a purely thermal basis [4].

The present study grew out of an interest in the use of heat in urological surgery and, in particular, in the use of ultrasound for controlled, localized production of heat in deep tissues [5]. From knowledge of the thermal sensitivity and acoustic absorption of tissues [4], it would be anticipated that thresholds for ultrasonic lesion production would be of the same order of magnitude for most tissues with high water content. This postulate was tested by comparing thresholds for rabbit liver, kidney, and testicle.

METHODS AND MATERIALS

The source of ultrasound in these studies was a one inch ceramic disk with a thickness to resonate at 2 MHz. The disk was cemented to the plane surface of a water cooled aluminum lens with a focal length of approximately 5 cm. The focal point was 0.5 cm beyond a hollow, plastic cone containing demineralized, degassed water for coupling to the tissue, Fig. 1. Contact between the cone and tissue and surface tension nicely retained the coupling water in the cone. Degassed water at room temperature was made available for flow into the cone and out over the surface of the organs, to further reduce the possibility of any air bubbles entering the cone. However, contact between the cone and the tissue was such that the flow of water was extremely small or nonexistent during the irradiation procedure. No cavitation monitoring equipment was used.

Total acoustic power was measured with a radiation pressure balance. The profiles of the sound beams at 2 and 6 MHz in the focal regions, as measured with a 70-μm-diam, Teflon coated thermocouple and confirmed with a hydrophone (Helix Ultrasonics, La Mesa, CA) are shown in Fig. 2. From the intensity distributions it follows that ratios of axial intensity (W/cm^2) at the focus to total power (W) are 30 cm^{-2} at 2 MHz and 140 cm^{-2} at 6 MHz. The ratio at 2 MHz was confirmed by direct measurements of axial intensity with a calibrated miniature hydrophone.

Three to four month old rabbits weighing 2.5 to 3.0 kgm were anesthetized with intravenously administered pentobarbitol at a dosage of 0.5 cc/kgm of bodyweight. The tissues to be irradiated were surgically exposed using 0.5% xylocaine when needed as a local anesthetic. The testicles were retracted from the scrotum and exteriorized through a low midline incision. The kidney and liver were mobilized and exteriorized through flank and upper midline incisions, respectively. To prevent localized heating at the far surface, the organ was backed by water sealed in a thin plastic film. The cone of the transducer was hand held in direct contact with the tissue surface. No direct method of temperature control was applied to the irradiated tissues. Because of this, the tissues were below body temperature during irradiation. The temperature of the tissues as measured by a thermocouple in a small hollow needle and a Bailey BAT 4 Thermocouple Thermometer are reported in the discussion. The tissues were irradiated with

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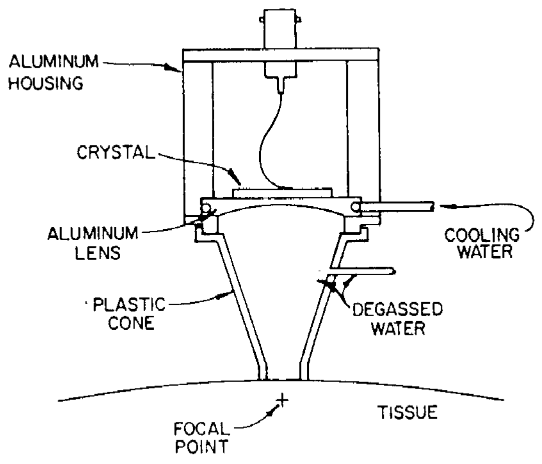

Figure 1. Focused Transducer Used in this Study.

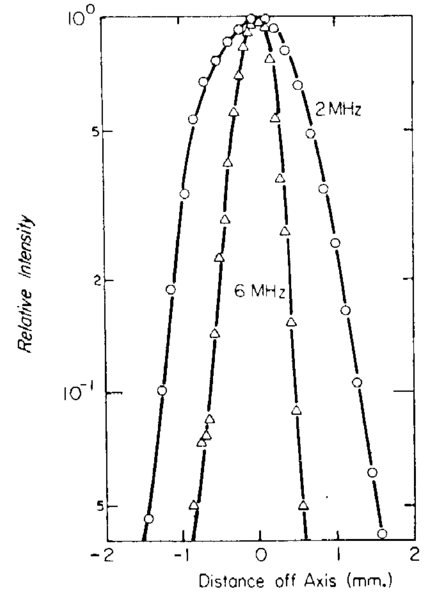

Figure 2. Beam Patterns at the Focus for the Transducer Used in this Study.

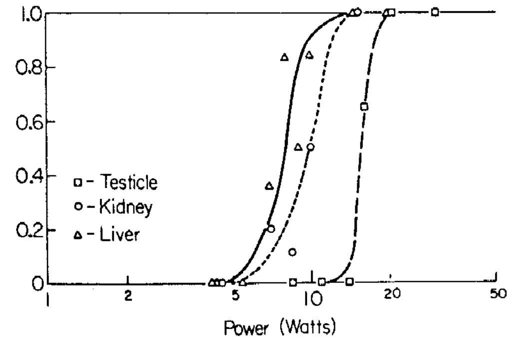

Figure 3. Probability of Lesion Occurrence. Each exposure was at 2 MHz for a duration of 15 s. For each power level, the ratio of the number of positive lesions to total number of samples exposed is plotted as the probability of the occurrence of a lesion. Threshold is that power for which the probability is 0.5.

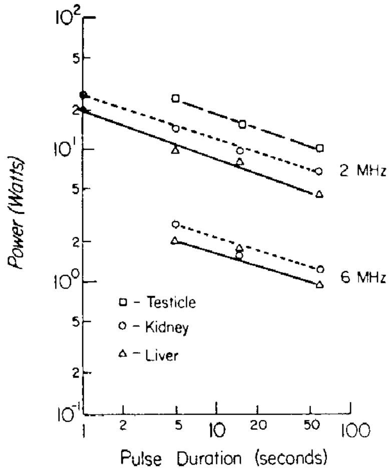

Figure 4. Power Thresholds for Focused Ultrasound in Rabbit Liver, Kidney, and Testicle. Approximate Temperatures were Liver 36°C, Kidney 37°C, and Testicle 31°C.

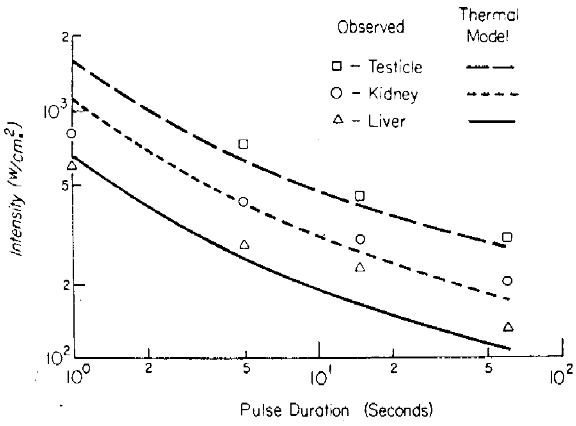

Figure 5. Intensity Thresholds at 2 MHz Compared to Threshold Curves as Predicted by a Thermal Model for the Action of Ultrasound on Tissue.[4]

single pulses of ultrasound with rectangular envelopes for durations of 1, 5, 15, and 60 s and varying intensities. The position of each of the several exposures per organ was marked with 6-0 surgical silk; the organs were returned to the body cavity and the incision closed. The animals were sacrificed three days later. The tissues were sectioned perpendicularly to the axis of irradiation, about 0.5 cm below the surface. The testicles were fixed in Bouin's solutions, and liver and kidney were fixed in Formalin. Microscopic sections were made, stained with hematoxylin and eosin, and examined for histological evidence of tissue destruction. The presence of a lesion was evidenced by a sharply defined area of tissue necrosis. Gross observation of the samples before sectioning revealed the lesion as a whitened area within the normal appearing tissue. Agreement between the gross and microscopic indications of tissue damage was essentially complete.

It is important to define the meaning of threshold in the context of these experiments. Because the activiation energy for thermal destruction of tissue is very large, the threshold for damage should be well defined. However, several factors in the experimental technique contribute to variability in the results. The most important of these is a small amount of movement of the tissue relative to the sound beam during the breathing cycle of the animals. Thus, even though conditions were as nearly identical as possible, lesions would be observed in only a fraction of the exposures near threshold. After several exposures at a given time and power, we could calculate a

TABLE I

ABSORPTION COEFFICIENTS AND BASELINE TEMPERATURES MEASURED AND USED TO CALCULATE INTENSITY THRESHOLDS AT 2 MHz

TISSUE	LIVER	KIDNEY	TESTICLE
ABSORPTION COEFFICIENT (cm^{-1})	0.14	0.08	0.07
TEMPERATURE (^{o}C)	36	37	31

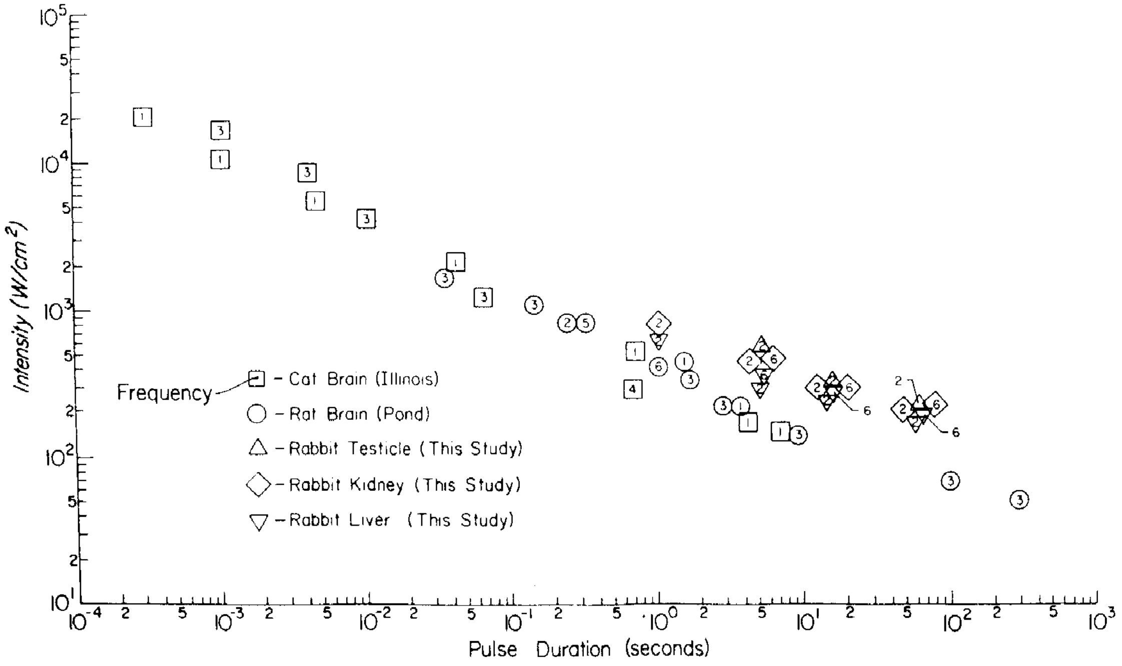

Figure 6. Intensity Thresholds for Focused Ultrasound. Rabbit kidney, liver, and testicle data from this investigation are corrected to correspond to a 37°C baseline temperature and compared with data for brain from previous studies.[1,2]

probability of lesion occurrence. This was done for several power levels to obtain a set of points for a probability vs. power curve. Fig. 3 illustrates a set of these curves for 15-s exposures at 2 MHz. The threshold is defined as the power at which the probability of finding a lesion is 0.5. Between 10 and 30 exposures were made to determine a single threshold power. By this procedure, thresholds could be determined in general to within ± 1 dB.

RESULTS

Fig. 4. summarizes the power threshold results for single pulse exposures of 2- and 6-MHz focused ultrasound for rabbit liver, kidney, and testicle. A frequency of 2 MHz provides a nearly optimum depth of penetration to develop localized heating in solid organs. However, because of a basic interest in the mechanism of the action of ultrasound on tissue, a number of observations were also carried out at 6 MHz. The 6-MHz power thresholds are much lower.

DISCUSSION

The ratios of axial intensity at the focus to the total power for the two frequencies were used to calculate intensity thresholds (see Fig. 6). The resulting intensities are nearly frequency independent. This has been found to be true in brain tissue [6]. The explanation [7] appears to lie in a fortuitous combination of two factors: 1) the absorption coefficient increases with frequency, and 2) the radius of the focal region decreases with frequency. The former increases the heat generation rate in the focal region, whereas the latter leads to more rapid heat diffusion from the focal region with increasing frequency. The two effects roughly cancel each other.

For exposure durations and intensities in the range of this study, it is generally believed that a thermal mechanism is responsible for tissue damage. If this is the case, there are several factors that may contribute to different thresholds among the tissues investigated. Variations in the thermal properties, including heat sensitivity, thermal diffusivity, activation energy for thermal damage, and the product of density and specific heat could be important. Two additional parameters of major importance are the absorption coefficient and the temperature at the start of irradiation. Thermal properties of various tissues measured by several investigators are compiled by Chato [8]. Though there are no data on testicular tissue, there seems to be very little variation in thermal diffusivity and the product ρc among brain, kidney, and liver tissues. Of the three tissues in this study, rabbit liver is the only one for which data are available for computation of an activation energy for thermal damage [9]. Indications are that any variation in heat sensitivity is insufficient to explain the differing thresholds [9]. The authors made rough attenuation measurements that show rabbit liver to have an attenuation coefficient at 2 MHz of about 0.14 ± 0.03 Np/cm, while values for rabbit kidney and testicle were about 0.08 ± 0.02 and 0.07 ± 0.03 Np/cm, respectively, where the indicated errors are one standard deviation. Thus differences in the absorption coefficients are a partial explanation for the differing thresholds.

Baseline temperatures for the tissues under irradiation conditions were somewhat lower than body temperature (40°C measured rectally). In particular, kidney and liver (measured 0.5 cm below the tissue surface) were 3° and 4°C below body temperature, respectively, while testicular temperature was 8° to 9°C below body temperature. The disparity between the exposed organ temperatures and the normal temperatures *in situ* is probably due to cooling related to exteriorization and contact of the organs with coupling water during irradiation. The testicle seems to have a very uniform temperature profile, while both liver and kidney exhibit increasing temperature with depth from the surface.

A thermal model [4] for the action of ultrasound on tissue was used to calculate intensity thresholds for lesion production on the tissues in this study. A value of 1.0 $\text{cal/cm}^3\ {}^\circ\text{C}$ was assumed for the product ρc, and a thermal diffusivity of 0.0014 $\text{cm}^2\text{/s}$ was used [10], [2]. Thermal sensitivity and an activation energy for thermal damage of 85 k cal/mole were obtained from data on rabbit liver [9]. As discussed above, baseline temperatures and absorption coefficients varied among the tissues and are summarized in Table 1.

In Fig. 5 the 2-MHz intensity thresholds as predicted by the thermal model and the experimentally determined thresholds are plotted. Considering only differences in baseline temperature and absorption coefficients among the tissues, the different thresholds are explained remarkably well. At the longer times and lower intensities the experimental data for liver are higher than predicted by the thermal model. This might be expected if there was movement of the sound beam relative to the tissue. In irradiations of liver, breathing of the animal made it particularly difficult to maintain relative position of the transducer and the tissue. Considering experimental errors and possible variation in thermal properties and activation energies, the agreement between predicted and experimentally determined thresholds is excellent.

Using the thermal model it was possible to calculate the effect of temperature on the threshold. By this means the experimentally determined thresholds were corrected to a baseline temperature of 37°C. Fig. 6 compares those results with brain tissue thresholds of previous investigations. Brain has been reported to have an absorption coefficient of 0.2 Np/cm at 2 MHz [10], [11]. That would explain the slightly lower thresholds observed for brain, if the activation energies for thermal lesions in brain and the tissues in this study are similar.

Thus it is concluded that thresholds for brain and tissues in this study are similar. Those differences which have been observed can be explained on the basis of a thermal model for the action of ultrasound on the tissues.

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