# Frequency dependence of threshold ultrasonic dosages for irreversible structural changes in mammalian brain

F. Dunn, J. E. Lohnes, and F. J. Fry*

*Bioacoustics Research Laboratory, University of Illinois, Urbana, Illinois 61801*
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Threshold ultrasonic single-pulse exposures for irreversible structural changes in the mammalian brain have been extended to include the frequencies 1, 3, 4, 4.5, and 9 MHz. The acoustic intensities of the delivered doses range from approximately $10^2$ W/cm$^2$ to $2\times10^4$ W/cm$^2$, with the corresponding exposure durations ranging from 2.5 sec to $5\times10^{-4}$ sec, respectively. The threshold dosage curves can be described by the relation $It^{1/2} = c(f, T)$, where $I$ is the acoustic intensity delivered to the site of the irreversible change, $t$ is the time duration of the single acoustic exposure, and $c$ is a weak function of frequency and possibly also of base temperature of the specimen.

Subject Classification: 80.40; 35.75.

The recent observation[1] that a simple relation describes the ultrasonic threshold dosages for irreversible changes in the mammalian brain with seeming independence of ultrasonic frequency has provoked several pertinent queries. The apparent lack of dependence of the threshold region upon frequency raises questions of the resolving power of the experimental method to reveal such subtle dependencies and of the involvement of the various physical mechanisms. An analysis of thermal processes, which assumes that the maximum temperature developed in the structurally altered volume is determined by the tissue absorption coefficient and by the spatial distribution of the acoustic intensity, yields a very weak frequency dependence of the threshold curves in the dosage region beyond 1-sec exposures.[2] Further debates recognize that such threshold data are an essential element in the establishment of safe operating standards for clinical and other applications.[3,4] This paper reports results of a study undertaken to investigate in greater detail the structure of the threshold dosage region. This is accomplished largely by increasing the number of frequencies at which exposures are made and by obtaining more specimens at each frequency such that greater precision ensues in the identification of the threshold region.

The technique employed, which involves exposing the cat brain to specific dosages of ultrasound, has been described in detail previously.[5] Briefly, the skull of the animal is removed, under deep anesthesia, to allow the sound to enter the brain unimpedded, though the dura mater is not opened. Degassed Ringer's solution is employed as the acoustic transmitting medium from the focusing transducer to the brain and the irradiation is performed with the brain temperature controlled at 37 °C. Numerous lesions can be placed in a single brain and the sites are selected such that the focal volume of one site does not overlap the focal volume of a neighboring site. In this regard, it is noted that a greater density of sites can be accommodated at higher frequencies, where the focal volume is smaller than at the lower frequencies, since the half-power beamwidth in all cases approximated a wavelength of sound in the tissue. As multiple irradiations are produced in a single brain, adequate time is allowed between the acoustic pulses to assure that the brain temperature does not deviate appreciably from the 37 °C. Generally, this means that approximately 4 min occur between successive exposures, though this is only approximate, as the position of the focal volume within the brain must be changed in three coordinate directions between each shot, a somewhat time-consuming procedure when performed manually. Following the complete irradiation procedure, the wound is closed and, for all of the data presented in this report, the animal is sacrificed 24 h later. The excised brain tissue is subsequently stained with both Weil and cresylecht violet and examined for histological evidence of alteration of brain tissue.

A successive approximation procedure is employed for determining the threshold loci. Specifically, for a chosen delivered acoustic intensity, the times of irradiation for the longest acoustic pulse yielding a negative effect and for the shortest acoustic pulse yielding a positive effect, i.e., to produce a lesion just observable with the light microscope, are sought. This procedure requires numerous specimens to establish a threshold point and Table I exhibits the number of animals employed at each frequency and the total number of exposures perpetrated. In this way it has been possible, at any chosen intensity, to identify the upper and lower bounds for irradiation times to within about 15%, i.e., the upper bound (minimum positive) exposure time is found to be no more than about 15% greater than the lower bound (maximum negative) over the entire range. The root-mean-square value of these two exposure times is then identified with the threshold loci.

Figure 1 shows the acoustic intensity of exposure versus the single-pulse exposure time; the plotted curves

TABLE I. Number of animals employed and total number of exposures at each frequency.

| $f$ (MHz) | No. of animals | Total No. of exposures |
|---|---|---|
| 1 | 10 | 112 |
| 3 | 27 | 301 |
| 4 | 7 | 80 |
| 4.5 | 2 | 24 |
| 9 | 16 | 167 |

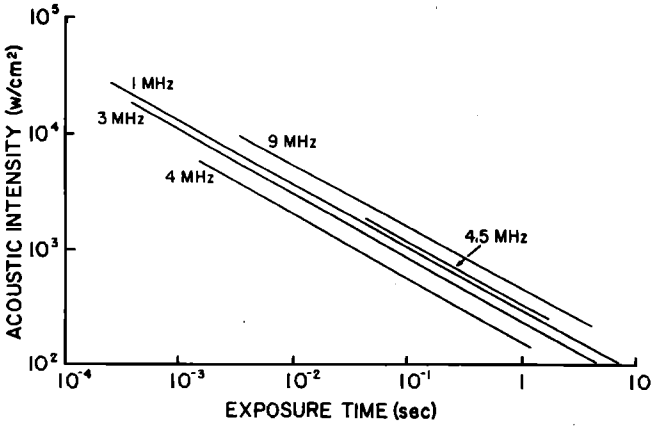


FIG. 1. Delivered acoustic intensity at the irradiation site versus single pulse duration of exposure to produce threshold lesions in mammalian brain.

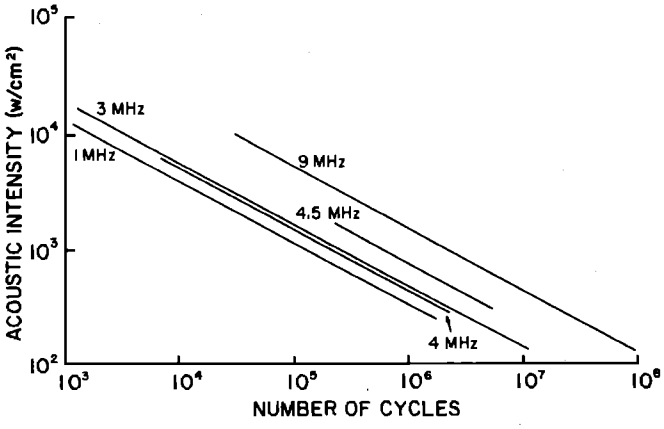


FIG. 2. Delivered acoustic intensity at the irradiation site versus total number of acoustic cycles to produce threshold lesions in mammalian brain.

are the threshold regions at the frequencies investigated. It is to be observed that all the frequencies exhibit straight lines of slope very nearly $-\frac{1}{2}$, on the log–log plot, and may be described by the relation

$$It^{1/2} = c(f, T), \tag{1}$$

where $I$ is the acoustic intensity at the site of the lesion, $t$ is the single pulse exposure time, and $c$ is at most a function of the ultrasonic frequency $f$ and the base temperature of the specimen $T$. The function $c$ is identified with the threshold intensity at 1-sec exposure and its logarithm is the intercept of Fig. 1. The delivered intensity is computed from the relation

$$I = I_0 e^{-\mu d}, \tag{2}$$

where $I_0$ is the unabsorbed acoustic intensity delivered by the transducer, $d$ is the site depth in centimeters, and $\mu$, the intensity absorption coefficient per unit path length of the tissue, is given by $\mu = 0.20f$, where $f$ is the frequency in megahertz. This frequency dependence of $\mu$ has been observed by numerous investigators,[6] but, for the purposes of this study, it was established further in the frequency range of interest by the two following methods. Firstly, single thermocouples were imbedded in the brain at the lesion locus and the transient thermoelectric method employed.[6] That is, $\mu$ was computed from

$$\mu = \frac{\rho C}{I}\left(\frac{dT}{dt}\right)_0, \tag{3}$$

where $\rho C$ is the heat capacity per unit volume of the tissue, $I$ is the acoustic intensity at the junction, and $(dT/dt)_0$ is the observed initial time rate of change of temperature at the junction associated with the phase of the response resulting from acoustic energy converted into heat by absorption in the surrounding tissue.[6] Secondly, ensembles of two and three thermocouples were imbedded in a linear array along the direction of propagation of the sound beam in the tissue and the acoustic intensity gradient observed, i.e., the absorption coefficient was obtained from

$$\mu = \frac{1}{d_1 - d_2}\log_e \frac{D_2}{D_1}, \tag{4}$$

where $D_1$ and $D_2$ are the responses from two thermocouples at depths $d_1$ and $d_2$, respectively, to a pulse of ultrasound of duration 0.1 sec. Both methods verified, and justified the use of, Eq. 2.

TABLE II. Statisitcally relevant data of Fig. 1.

| $f$ (MHz) | Number of threshold loci determining threshold curve | Slope† of threshold curve, $b \pm e$ (W/cm²/sec) | Threshold intercept function‡ $c = I_0 t_0^{b \pm e}$ (W/cm²/$t^b$) |
|---|---|---|---|
| 1 | 7 | $-0.536 \pm 0.059$ | $320^{+90}_{-70}$ |
| 3 | 12 | $-0.512 \pm 0.035$ | $300^{+52}_{-44}$ |
| 4 | 6 | $-0.456 \pm 0.064$ | $248^{+61}_{-49}$ |
| 4.5 | 4 | $-0.512 \pm 0.343$ | $347^{+114}_{-86}$ |
| 9 | 12 | $-0.512 \pm 0.037$ | $489^{+96}_{-68}$ |

†Mean slope $\pm t_{0.05(n)} \times$ standard deviation of slope, where $t_{0.05(n)}$ is the student $t$ factor for $n$ degrees of freedom and $P = 0.95$. $n = n' - 2$, where $n'$ is the number of data points used to calculate the slope.

‡Range of the function $c$ computed from above relation where $I_0$ is antilog of mean $\log_{10}$ threshold intensity and $t_0$ is antilog of mean $\log_{10}$ threshold exposure time.

Table II is a compilation of statistically relevant data regarding the plotted curves of Fig. 1, wherein it is seen that differences in slope are not suggested. However, a frequency dependence of the threshold regions, described by the function $c$ as slight displacement of the intercept of each of the threshold curves, is suggested. Figure 2, which may provide the link between data obtained under single-pulse exposure regimes and the repeated pulse regimes commonly employed in medical diagnosis, shows the intensity of exposure versus the total number of acoustic cycles and largely eliminates the maximum in sensitivity of the tissue at 4 MHz, as exhibited in Fig. 1. The form of the data suggests that the tissue strength (tensile, shear) may be the same for whatever physical mechanisms, e.g., thermal, cavitation, mechanical, or combinations of mechanisms,

which may be responsible for production of the irreversible structural changes in biological systems. It is interesting to observe that the curves of Fig. 2 resemble those for mechanical fatigue of solids, above the time-independent stress, as regards their stress-duration relations.[7]

Though the tissues of the central nervous system have been extensively studied as regards threshold dependencies, information on other tissues is beginning to emerge and it appears that irreversible structural change thresholds for rabbit kidney, liver, and testes are similar to that of the mammalian brain.[8] Such data on a variety of tissues and specimens are of the utmost importance from both the points of view of sagacious employment of this agent in medical practice and for the elucidation of the fundamental physical mechanisms involved in the production of such changes.

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*Present address: Department of Surgery, University of Indiana Medical Center, Indianapolis, IN 46207.

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