EXPOSURE LEVELS FOR ULTRASONIC CAVITATION IN MAMMALS

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ABSTRACT

Heat and cavitation are two mechanisms by which ultrasound is known to induce biological effects. Of the two, heat is reasonably well understood, but the role of cavitation in mammalian bioeffects needs further investigation. The levels for hind limb paralysis in the neonatal mouse from 1 MHz, continuous wave unfocused ultrasound have been investigated at 1 and 16 bars ambient pressure and at 10 and 37°C. Above approximately 150 W/cm^2 at 10°C and above approximately 60 W/cm^2 at 37°C the exposure duration for paralysis of 50 percent of specimens exposed increases with increased ambient pressure suggesting cavitational involvement. This temperature dependence is consistent with a cavitation mechanism. These levels are well above the time-averaged intensities employed in ultrasonic diagnosis and diathermy.

INTRODUCTION

Ultrasound is known to induce biological effects by thermal and nonthermal mechanisms. The thermal mechanism involves the conversion of mechanical energy associated with the sound wave into heat resulting in a significant temperature elevation. One nonthermal mechanism, responsible for many biological effects, is cavitation which involves the formation, oscillation, growth, or collapse of bubbles with attendant modification of surrounding materials. Of the two mechanisms, heat is reasonably well understood, but the role of cavitation in mammalian biological effects needs further investigation.

Cavitation is believed to be the dominant mechanism for production of biological effects in suspensions and solutions, plant roots and leaves, and in insects exposed to ultrasound (1,2). Transient cavitation has been shown to occur in mammalian systems at continuous wave (cw) exposures above approximately 1500 W/cm^2 at less than 1 s duration (3-5). However, bubbles have been detected in mammals during exposure to ultrasound at intensities less than 1 W/cm^2 (6-8), and this has been predicted by theoretical calculations based on growth of small gas nuclei by rectified diffusion (9). Also, theoretical predictions for water suggest the potential for transient cavitation from microsecond diagnostic ultrasound pulses (10-13). Yet recent evidence suggests that biological effects resulting from cavitation occur in mammals only at much higher intensities (14,15).

Frizzell et al. (14) reported that cavitation is involved in the production of hind limb paralysis in the mouse neonate exposed to 289 W/cm^2 cw ultrasound at 1 MHz and 10°C. They reported that at 144 W/cm^2 and lower there was no change in the exposure duration for paralysis in 50% of specimens exposed (t_{50}), between 1 and 16 bars ambient pressure. At 289 W/cm^2 the t_{50} nearly doubled with the increase in pressure. Since increased pressure tends to suppress cavitational effects, this was evidence for cavitation involvement at 289 W/cm^2 at 1 bar. In a continuing effort to determine the role of cavitation in mammals, a more complete analysis of the effects of pressurization has been conducted at 10°C and initial results have been obtained also at 37°C to determine the effect of temperature on the levels for cavitation.

METHODS

Neonatal mice, within 24 hours of birth, were irradiated with 1 MHz, cw, unfocused ultrasound at the third lumbar vertebral section, where the hind limb motor neurons are concentrated. Prior to irradiation, the specimens were anesthetized by lowering their body temperature to 10°C for treatment at that temperature or by administering intramuscular injections of ketamine HCl and xylazine at a dosage of 25 mg/kg for treatment at 37°C. Since the neonatal mouse is poikilothermic, its body temperature may be reduced to 10°C, without inducing any observable damage.

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The ambient pressure was raised to 16 bars by pressurizing the irradiation chamber with compressed air.

After irradiation the specimen was tested for hind limb paralysis by mechanical stimulation of the hind feet, tail, or stomach. The exposure duration for paralysis of 50 percent of the specimens exposed (t_{50}) was determined for each intensity level used. Approximately 120 animals were irradiated at each intensity level for which a t_{50} was determined. From these results an ED_{50} (effective dose - 50%) curve was plotted as intensity vs. exposure duration. Further details on the experimental methods may be found in a previous publication (14).

RESULTS

The ED_{50} ultrasonic exposure conditions for hind limb paralysis in the mouse neonate at 1 and 16 bars ambient pressure and at 10 and 37°C ambient temperature were determined and are shown in Figure 1. Examination of the data reveals that above a specific intensity level the ED_{50} exposure conditions are greater at 16 bars than at 1 bar ambient pressure whereas they are in common below that intensity. Since an increased ambient pressure tends to suppress cavitation, such changes suggest cavitational involvement. Thus, at 1 bar, cavitation may be involved in the resultant paralysis above approximately 150 W/cm^2 at 10°C, and above approximately 60 W/cm^2 at 37°C. The lower intensity for an effect of pressurization at the higher temperature is consistent with a cavitation mechanism. Presumably, below these intensity levels cavitation is not significantly involved, but heat is the dominant mechanism by which the paralysis occurs.

In order to assess the effect of the method of anesthesia on the outcome, the ED_{50} exposure conditions were determined using each of the two methods described above for several intensities at 10°C. As can be seen in Figure 1, it appears that the results are independent of the method of anesthesia.

The t_{50} at 86 W/cm^2 and 37°C was determined five separate times in order to better characterize the variability associated with its measurement. The mean of the five data sets was 0.663 s with a standard error of 0.005 s for a coefficient of variation of 0.8 percent. Repetitions at other intensities, involving different personnel and anesthetics, showed agreement within 3 percent.

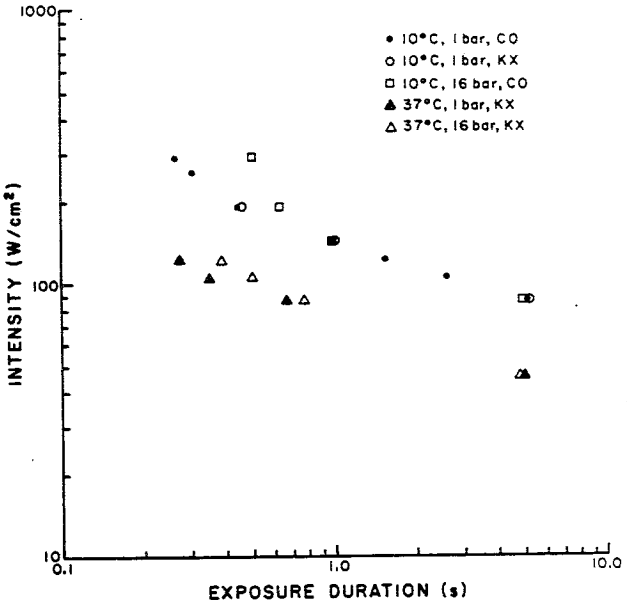

Figure 1. ED_{50} exposure conditions for hind limb paralysis in the mouse neonate at 1 MHz. The anesthetic was either ketamine HCl and xylazine (KX) or cooling to 10°C (CO).

CONCLUSION

The results presented suggest involvement of ultrasonically induced cavitation in the hind limb paralysis of the mouse neonate at intensities above approximately 150 W/cm^2 at 10°C and above approximately 60 W/cm^2 at 37°C. These intensity levels are well above the time-averaged intensities employed with diagnostic and diathermy ultrasonic systems. The levels are also well above those discussed in the American Institute of Ultrasound in Medicine "Statement on In Vivo Biological Effects" (16).

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