Ultrasound in Med. & Biol. Vol. 17, No. 1, pp. 65–69, 1991
Printed in the U.S.A.

0301-5629/91 $3.00 + .00

●*Original Contribution*

ABSORPTION IN LIVER AT THE FOCUS OF AN ULTRASONIC SHOCK WAVE FIELD

F. J. FRY,[†] C. R. REILLY,[†] K. A. DINES,[‡] M. R. ETCHISON[†] and E. J. TRAUNER[†]
[†]Indianapolis Center for Advanced Research, Inc., Indianapolis, IN and [‡]XDATA Corporation, Indianapolis, IN, USA

(*Received* 6 *December* 1989; *in final form* 25 *May* 1990)

Abstract—This experimental study is an extension of a previous investigation of finite amplitude ultrasound absorption at 1 MHz fundamental frequency in freshly excised rat liver at 37°C (Fry et al. 1989). The work reported here includes measurements of the absorption as a function of intensity under a variety of conditions (temperature, pressure, and tissue state). The maximum intensity employed in the investigation (700 W/cm^{-2}) corresponds to a shock parameter of approximately 1.7 based on previous characterization of the acoustic field which established that shock ($\sigma = 1$) occurred in the range 225 W/cm^{-2} to 275 W/cm^{-2} (Fry et al. 1989). Of the three temperatures chosen for the thermal study (30°C, 37°C, and 41°C), the only statistically significant differences ($p < 0.05$) in absorption were between the 30°C and 41°C data in the intensity range just above $\sigma = 1$ (300–500 W/cm^{-2}). The intensity-dependent absorption coefficient was also determined for excised liver under hyperbaric conditions and for liver *in situ* at 37°C. At a pressure of 350 psi, the absorption was generally less than at atmospheric pressure. *In situ* liver at 37°C had a lower absorption above 200 W/cm^{-2} than freshly excised liver, but the difference was only significant between 200 and 300 W/cm^{-2} and between 600 and 700 W/cm^{-2}.

Key Words: **Absorption, Nonlinear acoustics, Shock wave.**

INTRODUCTION

Numerous investigations of the absorption and attenuation of liver for linearly propagating waves have been published (Frizzell et al. 1979; Bamber and Hill 1979; Goss et al. 1979; Parker 1983; Lyons and Parker 1988). Previous studies with unfocused (Carstensen et al. 1981; Carstensen et al. 1982) and intense focused (Goss and Fry 1981; Fry et al. 1989) ultrasound at low megahertz frequencies have been concerned with determination of the absorption and attenuation coefficients in liver as a function of intensity at a single temperature. The experimental work reported here includes measurements of absorption of linearly and nonlinearly propagating waves under a variety of conditions (temperature, pressure, and tissue state). The absorption of tissue at 30°C, 37°C, and 41°C was measured to determine the effect of temperature. These measurements were made to compare the linear and nonlinear absorption at 37°C (normal body temperature) to those under hyperthermia conditions (41°C). Differences in absorption could be of significance to the practice of therapeutic hyperthermia. The measurements at 30°C were made to aid in comparing the absorption at normal body temperature to that at a much lower temperature typical of that used in some *in vitro* studies. In addition, the absorption of excised liver under hyperbaric conditions and of exteriorized liver have been completed to determine the effect of cavitation and tissue excision on the measurements. By elevating ambient pressure, cavitation effects can be greatly reduced. Knowledge of the presence or absence of cavitation is important in understanding sound field effects in body tissues subjected to shock waves. Since the majority of absorption measurements are made on excised tissue specimens, it is important to know how such measurements compare to those in which blood flow is intact. Exteriorizing the liver on the abdominal wall permits absorption measurements with intact blood flow.

MATERIALS AND METHODS

All fresh excised rat liver preparations and acoustic field measurement techniques for absorption studies have been previously documented (Fry et al. 1989). In summary, rat livers (approximately 5 mm thick and 1.5 cm in lateral dimension) were placed in degassed Ringers solution. Ultrasonic absorption measurements were performed using the transient thermoelectric technique. These measure-

ments started within 10 min after excision and were completed within 2 h. Studies have shown that absorption measurements remain essentially the same over this time period. A chromel-constantan thermocouple (76 μm diameter) was threaded into the liver so that the depth of the thermocouple junction was approximately 2 mm to 3 mm from the surface. Sound field intensity was determined using a 2 mm diameter steel ball radiometer (Dunn et al. 1977). Sound field intensity for the temperature study was based on steel ball calibrations at each temperature. All intensities quoted are spatial-peak temporal-peak (SPTP).

The equipment used for absorption measurements at atmospheric pressure was identical to that used previously (Fry et al. 1989) (Fig. 1). The 1 MHz spherical disk source had a diameter of 7 cm and a radius of convergence of 20 cm. The -3 dB focal region had an axial diameter of 9 cm and a lateral diameter of 4.65 mm in the linear intensity range (below 100 W/cm^{-2}). For the hyperbaric study, a specially constructed pressure tank was filled with mammalian Ringer's solution maintained at 37°C. The transducer housed in the pressure chamber utilized a duplicate of the transducer crystal used at atmospheric pressure. The transducer housing was modified to avoid a pressure drop across the transducer element which would distort the acoustic field. The pressure chamber had a thick glass window so that the steel ball calibration could be performed under the full pressure conditions. Freshly excised liver was suspended in the pressure chamber and attached to a three-axis orthogonal coordinate system. The axes of this system were mechanically controlled from outside the chamber. The liver with embedded thermocouple was located in the focal center of the 1 MHz sound beam by plotting the three-dimensional field using the thermocouple output. The absorption coefficient as a function of intensity was determined at atmospheric pressure prior to pressurization. The pressure was increased to 350 psi by introduction of nitrogen gas. The focus was relocated (there was a shift of no more than 0.2 mm in the focal center due to the increased pressure) and the absorption measurements were repeated. The pressure was then reduced to atmospheric pressure, the thermocouple recentered in the beam, and a final absorption measurement made.

For the exteriorized liver absorption coefficient measurements, the rat was anesthetized by injection of 10% thiopental and the liver exteriorized on the ventral side. The thermocouple was inserted in the liver in a manner similar to that used for the excised liver (Fry et al. 1989). The rat was partially submerged in the tank filled with 37°C Ringer's solution and the liver was positioned at the focus.

The absorption data were statistically analyzed to determine the relationship between absorption, intensity, and a variety of other factors (*i.e.*, temperature, pressure, and tissue state) using a two-factor analysis of variance (ANOVA). The intensity and the factor of interest in each experiment were the independent variables in the ANOVA. In all cases the ANOVA yielded a statistically significant ($p < .01$) interaction term. This indicated that the intensity–absorption relationship was not parallel for the factor

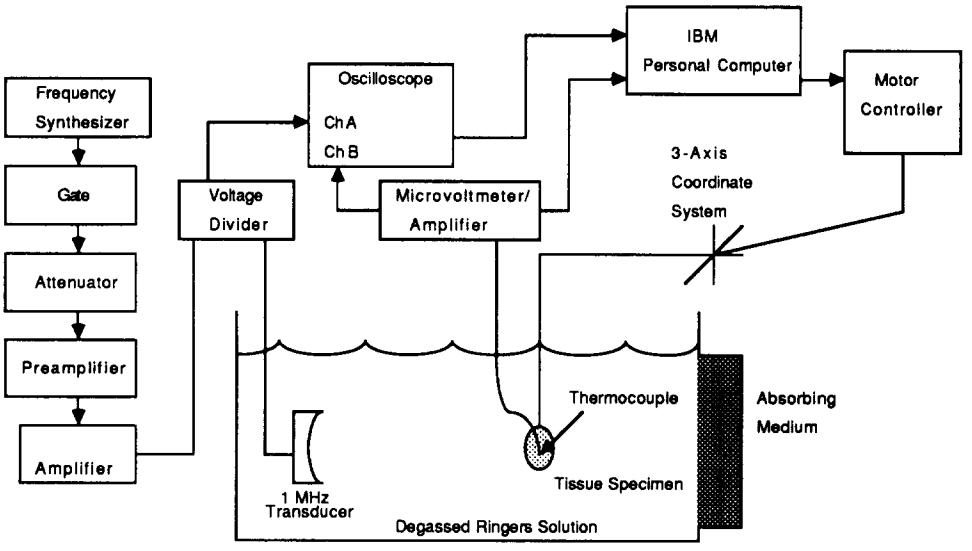

Fig. 1. Block diagram of system.

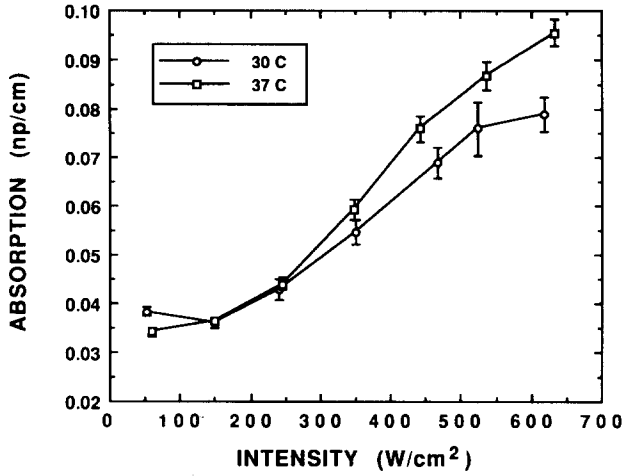

Fig. 2. Pressure absorption coefficient as a function of focal intensity at 30°C (○) and 37°C (□) with the standard error of the mean (SEM) shown for each intensity level.

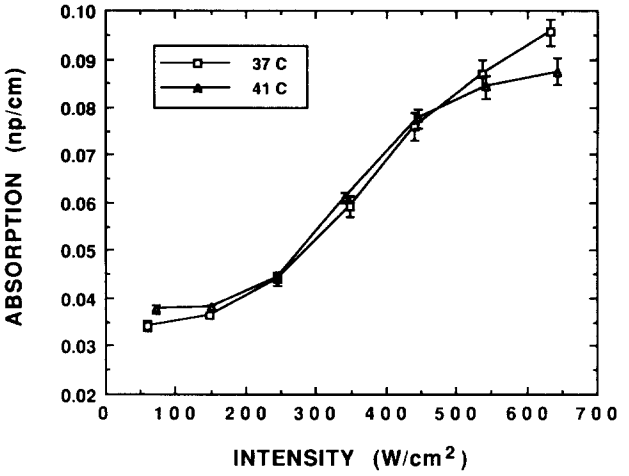

Fig. 4. Pressure absorption coefficient as a function of focal intensity at 37°C (□) and 41°C (△) with the SEM shown for each intensity level.

levels (*e.g.*, hyperbaric versus atmospheric pressure). Therefore, the *F*-tests for the overall test between the groups were not helpful in determining if the factors affected the value of the dependent variable. The data were divided into 100 W/cm^{-2} segments (*i.e.*, 0–99 W/cm^{-2}; 100–199 W/cm^{-2}, etc.). To determine whether the factor had an effect, mean differences were examined at each intensity level. Results were correlated for multiple testing using the Bonferroni inequality. Variance in the data is reported as the standard error of the mean (SEM). The data have been plotted at the mean values of intensity and absorption for each intensity interval.

RESULTS AND DISCUSSION

For the temperature study, measurements of the absorption as a function of intensity were performed at 30°C, 37°C, and 41°C. At linear intensity levels, the absorption coefficients at all three temperatures were 0.034 cm^{-1} to 0.038 cm^{-1} (Figs. 2–4). In general, between 100 W/cm^{-2} and 500 W/cm^{-2}, the absorption was lower at the lower temperatures. No significant differences in absorption were found between the data at 30°C and 37°C (Fig. 2) and between data at 37°C and 41°C (Fig. 4). Significant differences ($p < 0.05$) were observed at the two intensity levels be-

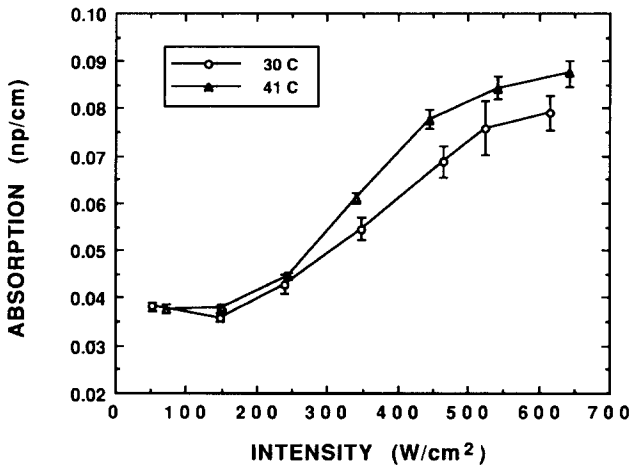

Fig. 3. Pressure absorption coefficient as a function of focal intensity at 30°C (○) and 41°C (△) with the SEM shown for each intensity level.

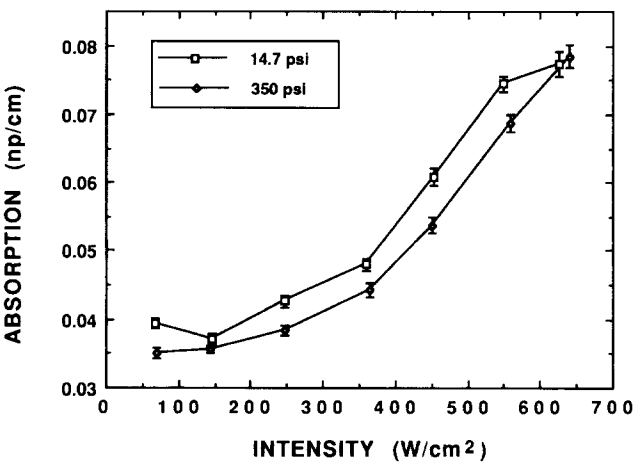

Fig. 5. Pressure absorption coefficient as a function of focal intensity at atmospheric pressure (□) and at 350 psi (◇) at 37°C.

tween 300 W/cm^{-2} and 500 W/cm^{-2} for the data at 30°C and at 41°C (Fig. 3). Absorption differences above 250 W/cm^{-2} are particularly of interest since this is above the σ = 1 intensity range (Fry et al. 1989). The mean ratio of the linear absorption coefficient in rat, bovine, and sheep liver at 25°C to that at 37°C has been reported to be in the range of 1.09 to 1.2 for 1 MHz irradiation (Frizzell 1984; Ibbini and Frizzell 1985). Our measurement of the ratio of the linear absorption at 30°C to that at 37°C was 1.12, although this difference was not found to be significant.

Absorption measurements at 37°C and 350 psi demonstrated a significant difference from measurements taken under atmospheric conditions at four intensity levels (0–99, 200–299, 400–499, and 500–599 W/cm^{-2}) (Fig. 5). The slightly higher absorption at atmospheric pressure may be the result of cavitation activity. Although the major vessels in the liver were clamped prior to excision and the tissue was excised and mounted in the holder while submerged in degassed Ringer's solution (Fry et al. 1989), the introduction of gas and its effect on the absorption cannot be completely discounted. Autolysis of the tissue during *in vitro* experimentation may be an additional source of gas in the tissue (Bamber and Hill 1979), although as previously stated no absorption measurements were made after 2 h post-excision.

The absorption in exteriorized (*in situ*) and in freshly excised liver showed significant differences at three intensity levels (Fig. 6). Between 0–99 W/cm^{-2}, the absorption in exteriorized liver was higher, while from 200–299 W/cm^{-2} and from 600–699 W/cm^{-2} the absorption in excised liver was higher. In general, above 125 W/cm^{-2} the absorption was slightly greater in excised liver.

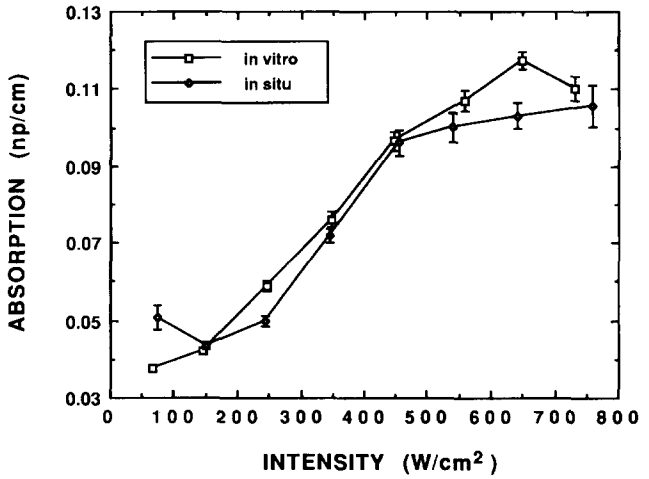

Fig. 6. Pressure absorption coefficient as a function of focal intensity for freshly excised (□) and exteriorized (◇) liver at 37°C.

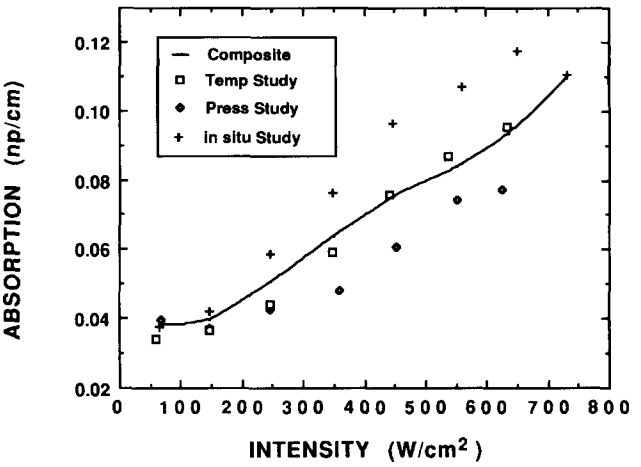

Fig. 7. The composite absorption coefficient as a function of focal intensity used in Fry et al. (1989) (——) is compared to the absorption coefficients in liver at 37°C from the temperature study (□), at atmospheric pressure from the hyperbaric study (◇), and for excised tissue from the tissue state study (+).

Over the course of this three-year study, three sets of absorption data on excised liver at 37°C and atmospheric pressure were collected. For the temperature study, data on absorption were collected at 37°C (Fig. 2). For the hyperbaric study, data were collected at 37°C and atmospheric pressure (14.7 psi) (Fig. 5). For the exteriorized liver study, data were also collected on excised liver at 37°C (Fig. 6). The linear absorption coefficients from these three studies ranged from 0.034 cm^{-1} to 0.037 cm^{-1} (Fig. 7). In the nonlinear intensity range, there was more variation between the three studies in the absorption values. The composite data are in general agreement with the data at 37°C. For thermocouple absorption measurements, the degree of repeatability seen over a three-year time span was reasonable. Data were gathered for each of the studies in a shorter time frame so that any differences in absorption can be attributed to the specific tissue environmental change.

The experimental absorption data in our previous investigation (Fry et al. 1989) were a compilation of results from the three aforementioned studies (temperature, hyperbaric, tissue state).

CONCLUSION

The absorption coefficients of liver have been determined as a function of temperature, pressure, and tissue state at 1 MHz for intensities up to at least 700 W/cm^{-2} ($\sigma \approx 1.7$). The composite absorption coefficient from the three studies at 37°C was 0.038 $\pm$ 0.001 Npcm^{-1} at linear amplitudes (below 100 W/cm^{-2}). The absorption in liver at 30°C was generally lower than at 37°C or 41°C. There was no significant difference in the absorption at 37°C and 41°C. These results indicate that differences in temperature in the 37°C to 41°C for the intensity range studied is not of importance to hyperthermia. The absorption of liver at atmospheric pressure was in general slightly higher than liver under 350 psi of pressure, suggesting a component of absorption due to air in the tissue. Cavitation at these intensities if present raises the absorption by at most some 10%, which might be considered to be somewhat minimal for therapeutic applications. The absorption in exteriorized liver with intact blood supply and excised liver were not greatly different. At the three intensity levels where the absorption differed, the excised tissue absorption was greater than the exteriorized tissue above σ shock intensities but less at intensities below 100 W/cm^{-2}.

Acknowledgments—The authors wish to acknowledge Dr. Barry Katz of IUPUI for the statistical analysis, Howard White for the fabrication of much of the equipment, and Cyndi Pote and Richard V. Chua for their assistance in manuscript preparation.

This investigation was supported in part by PHS Grant Number GM 30593 and the Indianapolis Center for Advanced Research.

REFERENCES

Bamber, J. C.; Hill, C. R. Ultrasonic attenuation and propagation speed in mammalian tissues as a function of temperature. Ultrasound in Med. & Biol. 5:149–157; 1979.

Carstensen, E. L.; Becroft, S. A.; Lau, W. K.; Barbee, D. B. Finite amplitude effects on the thresholds for lesion production in tissues by unfocused ultrasound. J. Acoust. Soc. Am. 70(2):302–309; 1981.

Carstensen, E. L.; McKay, N. D.; Dalecki, D.; Muir, T. G. Absorption of finite amplitude ultrasound in tissues. Acoustica 51(2):116–123; 1982.

Dunn, F.; Auerbach, A. J.; O'Brien, W. D. A primary method for the determination of ultrasonic intensity with the elastic sphere radiometer. Acoustica 38:58–61; 1977.

Frizzell, L. A. Temperature dependence of ultrasonic absorption in biological tissue. J. Ultrasound Med. 3(Suppl. 9):143; 1984.

Frizzell, L. A.; Carstensen, E. L.; Davis, J. D. Ultrasonic absorption in liver tissue. J. Acoust. Soc. Am. 65(5):1309–1312; 1979.

Fry, F. J.; Dines, K. A.; Reilly, C. R.; Goss, S. A. Losses in tissue associated with finite amplitude ultrasound transmission. Ultrasound in Med. & Biol. 15(5):481–497; 1989.

Goss, S. A.; Frizzell, L. A.; Dunn, F. Ultrasonic absorption and attenuation in mammalian tissues. Ultrasound in Med. & Biol. 5:181–186; 1979.

Goss, S. A.; Fry, F. J. Nonlinear acoustic behavior in focused ultrasonic fields: Observations of intensity-dependent absorption in biological tissue. IEEE Trans. Sonics and Ultrasonics SU-28(1):22–26; 1981.

Ibbini, M. S.; Frizzell, L. A. Temperature dependence of the absorption coefficient and the heat capacity of tissues. J. Ultrasound Med. 4(Suppl. 10):115; 1985.

Lyons, M. E.; Parker, K. J. Absorption and attenuation in soft tissue II—Experimental results. IEEE Trans. UFFC 35(4):511–521; 1988.

Parker, K. J. Ultrasonic attenuation and absorption in liver tissue. Ultrasound in Med. & Biol. 9(4):363–369; 1983.