In vitro ultrasonic heating of fetal bone

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The temperature increase measured *in vitro* in human fetal femurs exposed to 1 MHz, continuous wave ultrasound at 37 °C is reported. The temperature is measured with a thermocouple probe and is given for several gestational ages. The initial rate of the temperature increase in the specimens is evaluated and compared to known values of absorption in soft tissue. For example, the initial rate of temperature increase in the 108-day gestational age specimen resulting from exposure to ultrasound is 30 times greater in the fetal bone than that of soft tissue with an absorption coefficient of 0.05 cm^{-1}.

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INTRODUCTION

Although the use of ultrasound as a diagnostic tool in obstetrics has become ubiquitous, concern that deleterious effects may occur continues (AIUM, 1988). A physical mechanism by which biological effects could, under some exposure conditions, be produced is the deposition of heat in the tissue as a result of energy absorbed from the acoustic wave (Dunn *et al.*, 1969). Knowledge of the absorption coefficient enables calculations to be made of the temperature increase, using the diffusion or the bioheat equations, which then allows the thermal effects to the tissue to be assessed. Although values of the absorption coefficient for many tissues have been reported, including some attenuation values for bone (Goss *et al.*, 1978, 1980), little is known about the acoustic absorption in fetal bone and its variation with fetal development. Thus good estimates of the temperature increase in and near fetal bone during exposure to ultrasound cannot be made. The anisotropic, heterogeneous nature of bone is known to render measurement of the elastic constants difficult (Yoon and Katz, 1976a,b; Katz and Yoon, 1984; and Henneke and Jones, 1976). The measurement of attenuation and absorption in bone is likewise difficult. The absorption is likely to be a function of the type of wave as well as direction of propagation. Also, knowledge of acoustic intensity values at the site of temperature measurement, needed to calculate the absorption (Dunn *et al.*, 1969), is inadequate. Calculation of the absorption from the temperature increase data also requires knowledge of the heat capacity C_p (Dunn *et al.*, 1969), at the site of interest, which is not available for fetal bone.

In the absence of knowledge of absorption in fetal bone, the measured temperature increase resulting from exposure of the specimen to ultrasound is useful for assessing thermal effects. In this study, the temperature increase in human fetal femurs exposed, *in vitro*, to 1 MHz, continuous-wave (cw) ultrasound is presented. The transient thermoelectric method, originally developed for measuring the absorption coefficient in soft tissues and liquids, is employed to measure the temperature increase (Fry and Fry, 1954a, b). The specimens represent the range of gestational ages from 59–108 days. The temperature increase measured over an extended period of time, as well as the time derivative of the temperature at 0.2 s following initiation of exposure to a square acoustic pulse, was measured. The time necessary for the temperature to increase by 1 °C is considered a useful parameter and is presented for the described exposure conditions (AIUM, 1988).

I. METHODS

The fetal femur specimens were obtained from the Central Laboratory for Human Embryology, University of Washington, Seattle, WA. The specimens were frozen and packed in dry ice, shipped via overnight mail, and stored at − 70 °F prior to the measurement procedures. The fetal femurs were exposed to 1 MHz, cw ultrasound using the transient thermoelectric method (Dunn *et al.*, 1969). All soft tissue attached to the bone was removed. A constantan–chromel thermocouple junction of diameter 25 to 40 μm, lap soldered to yield an axial dimension of approximately 300 μm, was the temperature sensor. The thermocouple was positioned midway along the length of the femur in the diaphysis with the aid of a 30-Ga. hypodermic needle, o.d. 0.31 mm. The needle is readily inserted by pushing for the earlier gestational age specimens (59–78 days), but it is necessary to drill a hole with a #80 drill bit (0.33-mm diameter) to enable insertion in the harder bone of later gestational age specimens. The thermocouple junction is positioned in the specimen with the aid of a dissecting microscope. The specimen is then submerged in physiological Hank's solution to allow fluid to fill the space created by the insertion process. The specimen is supported in a special holding device that does not interfere with the incident ultrasound field and is potted in 3% Bacto–agar (Diffco Laboratories). The agar is heated and dissolved at 78 °C, poured as a liquid into the holding device, with the specimen present, at 38° to 40 °C, and solidifies at 35 °C. The agar, having negligible acoustic absorption and a sound speed nearly that of water (Burlew *et al.*, 1980), serves the purpose of minimizing the removal of heat, produced by the absorption of sound energy by the specimen, by convection in the ultrasound transmission fluid. The dimensions of the agar potting are $3 \times 5 \times 8$ cm, with the 5×8-cm plane lying in the plane of the *xy* axes, and

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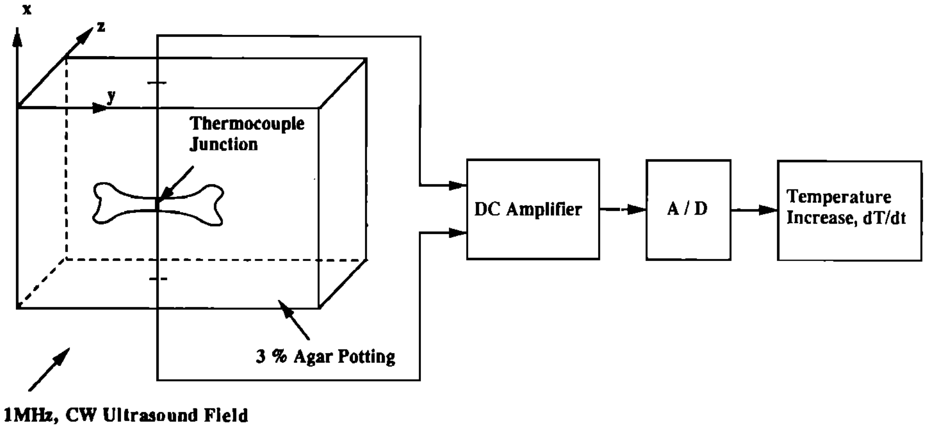

FIG. 1. Schematic representation of the experimental procedure.

normal to the direction of the incident ultrasonic field, as shown in Fig. 1. The femur cross section is approximately elliptical, and the specimen is oriented with the major axis parallel to the direction of the incident field.

The holding device, containing the potted specimen, is submerged in a gently stirred bath of degassed mammalian Ringer's solution maintained at 37 °C during the measurement procedures. The specimen is irradiated with ultrasound, and the change in the thermal emf, developed by virtue of the temperature increase at the thermocouple junction relative to the "cold junctions" outside the acoustic beam, is amplified, digitized, and stored for later analysis. A schematic representation of the preparation and measurement procedure is shown in Fig. 1.

Two transducers were used to obtain the data presented in Table I. The 59- and 89-day specimens were irradiated at the focal point of a 1 MHz, 5.08-cm aperture, focused PZT-4 transducer, with a radius of curvature of 15 cm and 3- and 6-dB beamwidths of 0.5 and 0.6 cm, respectively. All remaining specimens were irradiated with an unfocused, 1-MHz, 2.54-cm aperture, PZT-4 transducer with 3- and 6-dB beamwidths of 1 and 1.5 cm, respectively, at the field position

TABLE I. Temperature increase in the fetal femur exposed *in vitro* to cw ultrasound (°C).

Gestational age (days)	Irradiation time (s)	Diameter[a] (± 0.5 mm)	Length (± 2 mm)	Intensity (W/cm^2)				
				0.1	0.5	1	5	10
59	20	0.5	11		0.05	0.10	0.48	0.96
67	20	0.75	15		0.13	0.27	1.60	3.35
	35			0.03	0.15	0.31	1.83	3.89
78	20	1.2	17	0.06	0.34	0.69	3.94	8.7
	35			0.07	0.39	0.79	4.6	10.2
	50			0.08	0.42	0.85	5.0	11.3
83	20	1.2	24		0.66	1.31	6.5	14.0
	35				0.78	1.53	7.6	16.3
	50				0.86	1.68	8.3	17.8
	60				0.90	1.74	8.7	18.4
89	20	1.5	27		0.69	1.39	7.0	14.1
	35				0.78	1.55	7.9	15.6
	50				0.82	1.64	8.4	16.8
	60				0.84	1.69	8.6	17.2
91	20	1.8	30		0.89	1.79	8.9	19.3
	35				1.07	2.14	10.6	23.0
	50				1.19	2.39	11.8	25.4
	60				1.26	2.54	12.4	26.6
	180				1.59	3.19	15.3	32.6
108	20	3.3	38	0.31	1.48	2.92	14.9	28.1
	35			0.38	1.75	3.49	18.3	35.0
	50				1.92	3.85	20.4	40.0
	60			0.41	2.01	4.0	21.3	43.1

[a] The femur cross section is approximately elliptical. The dimension given is the average of the major and minor axes.

selected. Because of the small diameter of the 59-day specimen, less than 1 mm, relative to the half-power beamwidth of the focused transducer, the difference between the temperature increase that would have been measured with the unfocused transducer and that measured with the focused transducer is negligibly small for the exposure time shown. The temperature increase was measured in an 83-day specimen irradiated first with a focused and then an unfocused transducer to determine the difference between the two transducers in the heating of the later gestational age specimens. The spatial peak, temporal average (SPTA) intensities were the same in both cases. It was found, for example, that the temperature increase resulting from irradiation with the focused transducer was 24% less, after a 60-s irradiation, than that measured using the unfocused transducer.

II. RESULTS AND DISCUSSION

Table I lists the temperature increases measured in the specimens at specific exposure intensities, as well as the length and diameter of the various gestational age specimens studied. The error in the measured temperature is less than 3%. The exposure intensities were determined in the free field in degassed mammalian Ringer's solution with a thermoelectric probe that had been calibrated against a steel sphere radiometer (Dunn *et al.*, 1977). The temperature increase was measured for two different 108-day gestational age specimens in order to assess the repeatability of the entire procedure, which yielded a difference in the temperature increase between the two specimens of approximately 6% for the range of times listed in Table I.

The temperature increase of the 78-day specimen, irradiated with the unfocused transducer, versus intensity is shown in Fig. 2, where it is apparent that the temperature increase is nearly linear with exposure intensity in the range of 0.1–10 W/cm^2. Pressure amplitude measurements with a wideband hydrophone (NTR Systems, Inc.), with a 1- to 20-MHz bandwidth, in degassed mammalian Ringer's solution, showed the second harmonic component in the field of the unfocused transducer to be down 10 dB from the fundamental at an intensity of 10 W/cm^2, while the second harmonic was down 24 dB from the fundamental at 0.5 W/cm^2. The linearity of the temperature rise with intensity for the two specimens irradiated with the focused transducer, shown in Fig. 2 for the 89-day specimen, is a result of the second harmonic component being down 25 dB from the fundamental at 10 W/cm^2 at the focal point.

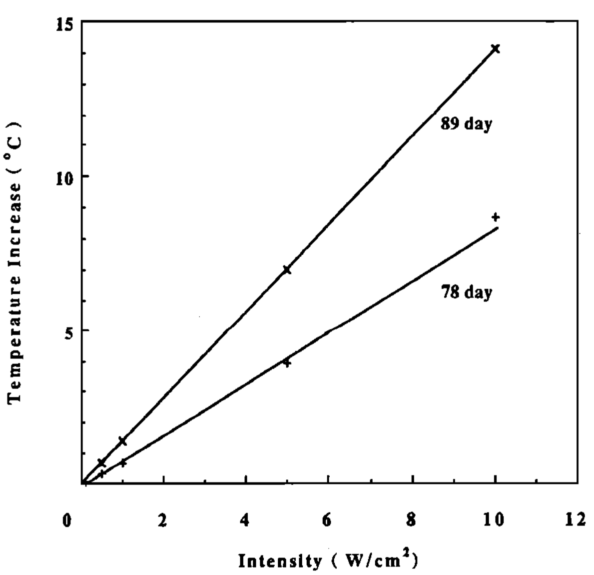

FIG. 2. Temperature increase at 20 s following the initiation of the ultrasound pulse *versus* intensity for 78- and 89-day specimens.

The temperature increase measured at long times in the femur specimens is a function of the intensity at the point of measurement, thermal diffusivity, amount of acoustic energy converted to heat, i.e., absorption, and the total heating volume of the specimens. The thermal diffusivity and absorption are expected to vary with gestational age. A measure is desired to identify the portion of the temperature increase that is not dependent on the heating volume of the specimen, as gestational age increases. For soft tissue, the temperature increase due to absorption is separated from the tissue volume and intensity by assuming knowledge of the acoustic intensity in the tissue, and evaluating dT/dt, the time derivative of the temperature, at a time at which heat conduction is negligible. The problem is more complex in the case of a fetal femur specimen. The ultrasonic intensity distribution in the specimen is unknown, and absorption in compact bone is expected to be different than that in the inner bone lumen. Further, the total dimensions of the femur specimens at the point of temperature measurement are smaller than typically encountered for soft tissues. In the case of the fetal bone, the quantity dT/dt for negligible heat conduction will be a function of bone mineral content, heat capacity, density, and intensity at the site of temperature measurement, all of which vary with gestational age. Thus the acoustic intensity at the site of temperature measurement will vary with gestational age because of the changing acoustic properties, as well as the changing dimensions of the bone. Although the quantity $I_0^{-1}\, dT/dt$, where I_0 is the free-field SPTA intensity, evaluated when heat conduction is negligible, is not independent of the specimen size or shape, it provides a useful measure of the variation in heat deposition with gestational age that is not dependent on the total heating volume of the specimen.

A second-order polynomial curve is fit to the digitized measured temperature over the first 0.5 s for the 59- and 67-day gestational age specimens, and over the first 1 s for the remaining specimens. The derivative of the temperature increase at 0.2 s, normalized to the SPTA intensity incident on the specimen, as a function of the gestational age, is shown in Fig. 3. The quantity $I_0^{-1}\, dT/dt$ at 0.2 s shown in Fig. 3 has been measured for a single specimen of the gestational ages available; thus no error bars are shown. The error in the determination of the gestational ages is $\pm$ 2 to 4 days, depending on the gestational age (Shephard, 1989).

The time derivative of the temperature is evaluated at 0.2 s herein, as opposed to the more common 0.5-s delay when using the transient thermoelectric method to measure the absorption coefficient in soft tissue, in order to minimize errors introduced by heat conduction (Goss *et al.*, 1977). It

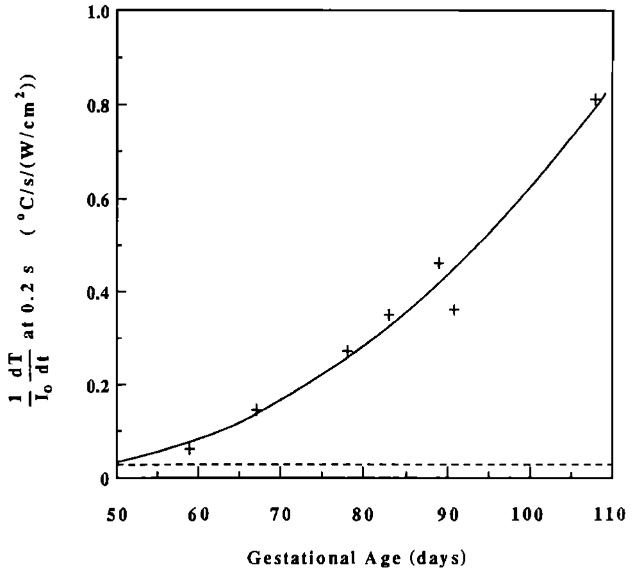

FIG. 3. Time derivative of the temperature, normalized to the incident intensity, *versus* the gestational age of the specimens. The solid curve is a quadratic least-squares fit to the measured data. The dashed line is the value obtained for soft tissue with an absorption coefficient of 0.05 cm^{-1}.

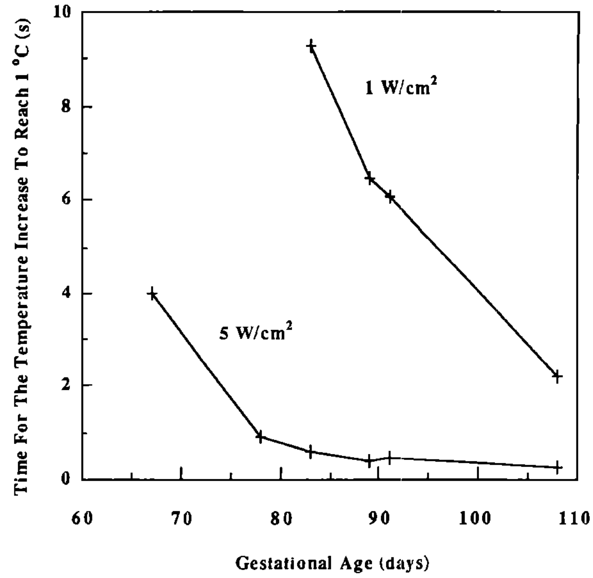

FIG. 4. Time of ultrasonic exposure required for the temperature increase to reach 1 °C *versus* gestational age.

has been shown for soft tissues, that appreciable errors can result in evaluating the derivative of the temperature while assuming no heat conduction, if the thermocouple junction is placed too near the boundary between the absorbing specimen and nonabsorbing coupling medium (Parker, 1985). It has been determined that a thermocouple junction placed 1 mm or deeper in soft tissue is consistent with the assumption concerning negligible heat conduction away from the junction at 0.5 s (Goss *et al.*, 1977; Parker, 1985). As regards evaluating the time derivative of the temperature of the fetal femur specimens, the important dimension is the diameter of the bone at the location at which the temperature is measured. The diameter of the fetal femurs ranges from 0.5–3.3 mm for the gestational ages studied. The small size of the specimens causes the value of $I_0^{-1}\, dT/dt$ to be sensitive to the placement of the thermocouple junction in the specimen. The placement of the thermocouple junction too near the bone surface can result in a significantly different measured $I_0^{-1}\, dT/dt$. In addition, the functional variation of the intensity over the femur, in the vicinity of temperature measurement, although unknown, is not expected to be slowly varying, and, hence, would shorten the linear portion of the temperature increase after the initiation of the ultrasonic pulse.

The contribution of the viscous heating, which results from the relative motion of the thermocouple wire and the bone, to the temperature derivative at 0.2 s is negligible. The size of the hole left by the insertion of the thermocouple in the bone is several times larger than the diameter of the thermocouple wire. Contact between the bone and the thermocouple wire occurs over only a fraction of the circumference of the wire. The resulting heating distribution is appreciably smaller than would occur in the case of soft tissue where the tissue is presumed to relax to its original conformation to make contact around the entire periphery of the thermocouple wire. The time dependence of the viscous heating in the case of the bone specimens should then be small at times shorter than the 0.1 s of the same response obtained for soft tissue (Fry and Fry, 1954a, b). The measurements show the rapid rise time in the temperature response associated with the viscous heating to be approximately 0.05 s, which is 25% of the time at which the derivative of the temperature is evaluated. The above ratio of the fast rise time to the time at which the derivative is evaluated is comparable to the ratio for measurements in soft tissues.

The time required for the temperature to increase 1 °C for a specified set of ultrasonic exposure conditions is considered important in view of the fact that the diurnal variation in the body temperature of the mother is of this magnitude. Thus ultrasonic exposure conditions, in which the primary consideration for deleterious effects to the fetus is heat deposition, are considered to be without risk if such a temperature increase is not exceeded. The irradiation time necessary for the temperature to increase 1 °C in the specimens studied is shown in Fig. 4 for incident intensities of 1 and 5 W/cm^2.

III. CONCLUSION

The temperature increase data reported in this study can be compared to that expected for soft tissue by computing $I_0^{-1}\, dT/dt = 2\alpha/\rho C_p$, where I_0 is the SPTA intensity, for nominal soft tissue values of α, ρ, and C_p (Goss *et al.*, 1978, 1980; Sekins and Emery, 1982). For $\alpha = 0.05$ cm^{-1}, and $\rho C_p = 3.78$ J/ °C/cm^3, $I_0^{-1}\, dT/dt = 0.026$ °C/s/(W/cm^2). This value of $I_0^{-1}\, dT/dt$ can then be compared directly with the values measured for the fetal bone studied as shown in Fig. 3. The values measured for the 59- and 108-day specimens are approximately 2 and 30 times greater, respectively, than the soft tissue value. The temperature increase measurements presented have been for a single orientation of the femur specimen with respect to the incident ultrasound field. It is likely that the quantity $I_0^{-1}\, dT/dt$, for negligible heat conduction, will be different for other orientations.

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