Mar (5)
Br. J. Cancer (1982) **45**, Suppl. V, 55-58

NONLINEAR ULTRASONIC PROPAGATION IN BIOLOGICAL MEDIA

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Summary.—The nonlinearity parameter B/A for several biological materials was determined by measuring the amplitude of the second harmonic pressure as a function of distance from the source and the amplitude of the fundamental at the source. The B/A values for bovine serum albumin and haemoglobin solutions were found to increase approximately linearly with solution concentration. Blood and homogenized liver exhibit a B/A value similar to a haemoglobin solution of the same dry weight, but whole liver has a greater B/A value.

THE USE of ultrasonic energy in medical diagnosis and therapy continues to increase. In diagnosis it is desired to obtain accurate and complete information of a medium, by ultrasonic means, without effecting changes in that medium. In therapeutics it is essential to know how to predict the response of a medium to ultrasonic propagation and to be able to determine accurately deposition of energy in the medium. For both these purposes it is of importance to know in detail the manner in which ultrasonic energy propagates through biological media.

It is well known that the fundamental mechanisms of sound propagation in fluid media are non-linear (Beyer & Letcher, 1969). Because of the analytic complexities of dealing with non-linear phenomena, and because a large class of phenomena may be so treated pragmatically, linear relationships have been assumed to be applicable (Kinsler & Frey, 1962). However, experimental evidence is accumulating to indicate that such treatment may not always be appropriate (Carstensen *et al.*, 1980, 1981; Goss & Fry, 1981; Law *et al.*, 1981). The non-linearity of propagation is due in part to deviation of the medium from linear Hooke's law stress-strain behaviour and in part to the amplitude of the acoustic wave disturbance. If the equation of state (the stress-strain relationship) is represented as a Taylor's series and only the quadratic and linear terms considered, the ratio B/A of these respective coefficients may be employed as the parameter to describe the non-linearity of the medium.

As a result of this non-linearity, an originally sinusoidal wave becomes distorted as the wave propagates. The amount of distortion increases with the intensity of the wave, the distance travelled and the frequency of the fundamental. In the frequency domain, the distortion process implies the generation of harmonics at the expense of energy extracted from the fundamental. Since high frequency components of an acoustic wave are absorbed more readily than are the lower frequency components, the effective absorption of a distorted wave is greater than that of a monochromatic wave of the fundamental frequency. Because of the greater absorption, the rate of energy deposition from a distorted wave within the propagating medium is greater than that from an undistorted wave, implying increased heating to an object being irradiated. For very intense waves, the increased absorption of the wave leads to acoustic saturation and a corresponding limit to the amplitude of the propagating acoustic radiation (Beyer & Letcher, 1969).

In order to assess the consequences of

the acoustic non-linearity in biological and medical applications of ultrasound, it is important to determine the degree of non-linearity in biological media and to consider methods of observation having the potential for *in vivo* measurements. This paper reports the results of an investigation of the non-linearity parameter B/A in solutions and suspensions of biological materials and in excised liver tissue.

ACOUSTIC METHOD

It has been shown that, for a quadratic pressure-density relationship, and in the absence of dissipation, the following relation emerges between the nonlinearity parameter B/A and measurable quantities (Adler & Hiedemann, 1962):

$$\left.\frac{p_2(x)}{x p_1^2(0)}\right|_{x p_1(0)\to 0} = (\mathrm{B/A}+2)\,\frac{\pi f}{\rho_0 c_0^3}$$

where $p_2(x)$ is the second harmonic pressure amplitude at the distance x, $p_1(0)$ is the pressure amplitude of the fundamental at the source, f is the frequency of the fundamental, ρ_0 is the undisturbed density of the medium, and c_0 is the infinitesimal wave phase velocity. Though this solution is not strictly applicable for a medium with absorption, such as tissues, numerical calculations (Haran, M. E., private communication) and experimental measurements have shown that, in an absorbing medium, the parameter $p_2(x)/xp_1^2(0)$ decreases exponentially with distance when the source pressure and the distance are small, allowing extrapolation to the point $x=0$, where the above relationship is valid. Initial determinations of the parameter $p_2(x)/xp_1^2(0)$ versus distance, in a bovine serum albumin solution, have verified this exponential relationship (Law *et al.*, 1981).

Fig. 1 is a diagram of the measurement system. A 3·4 MHz, $\frac{1}{2}''$ diameter piezoelectric sound source was coupled to a $\frac{3}{4}''$ diameter wideband receiver directly through the sample whose B/A value was to be determined. Both the source and receiver were calibrated in sodium chloride solutions, covering the range of acoustic impedances exhibited by the samples to be studied, using a radiation force technique (Fry & Dunn, 1962). The source was driven with a pulse modulated RF signal whose pulse duration was long enough to allow the system to reach equilibrium, but short enough to avoid standing wave difficulties. The received signal was spectrally analysed and the second harmonic amplitude was recorded at different source-receiver separations. Using water, ethylene glycol and glycerin for comparison, it was found that B/A values obtained by this method agreed with those of the thermodynamic method (Coppens *et al.*, 1965) to within 10% (Law *et al.*, 1981). Though the thermodynamic method has been used for most measurements of B/A, the method described in this report has the potential to be usable for *in vivo* measurements.

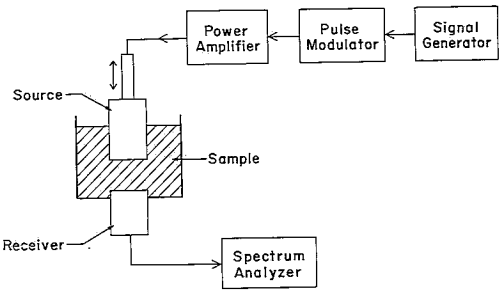

FIG. 1.—Schematic diagram of the measurement system.

RESULTS

Different concentrations of bovine serum albumin solutions, which have velocity and absorption values similar to tissue (Goss & Dunn, 1974) and so may be considered as homogeneous and less structured models, were prepared by dissolving the powdered solid (Sigma Chemical Co., St Louis) in degassed water. Fig. 2 shows the B/A values for such solutions at 30°C. (The value of B/A for water at 30°C is 5·2). It is seen that B/A increases approximately linearly with the concentrations of the solutions.

Haemoglobin solutions, obtained by first separating the red cells from porcine blood by centrifugation, lysing the cells with toluene and finally removing the cellular debris by high speed centrifugation, have also been studied. As seen in Fig. 3, haemoglobin solutions were found to behave much like solutions of bovine serum albumin.

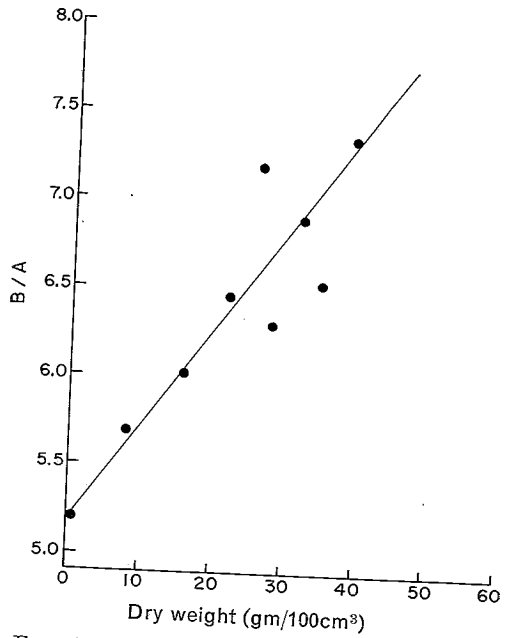

FIG. 2.—Values of B/A for bovine serum albumin solutions at 30°C versus dry weight (concentration).

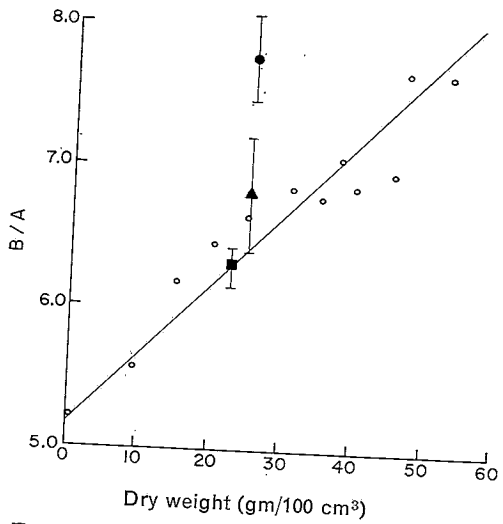

FIG. 3.—Value of B/A for haemoglobin (extracted from porcine blood) solutions at 30°C (○), whole porcine blood at 30°C (■), homogenized liver at 23°C (▲), and whole liver at 23°C (●) versus dry weight.

The B/A value for blood, which is more structured than an aqueous protein solution, but is homogeneous and isotropic on a macroscopic scale, is shown in Fig. 3. The porcine whole blood was treated with 3% sodium citrate, as an anticoagulant, and was studied within 2 h of slaughter. Whole blood contains about 12% haemoglobin, and about 7% plasma proteins (Attinger & Michie, 1976), with a small quantity of other solutes. Thus, the content of whole blood is physiologically significantly different from that of haemoglobin solutions, though the B/A value of whole blood appears to be similar to that of a haemoglobin solution of the same dry weight content.

Homogenized and whole beef liver provide an opportunity to assess the influence of tissue architecture upon B/A. The liver samples were obtained fresh from the slaughter house, stored at 5°C and studied within 48 h. Homogenates were prepared by liquefying beef liver in a blender for about 1 min. The B/A value determined for liver homogenate is seen in Fig. 3 to be slightly greater than a haemoglobin solution of corresponding dry weight.

In order to make measurements of $p_2(x)$ in whole beef liver, a sample of original thickness about 3 cm comprised the pathway between the transmitting and receiving transducers, which was successively reduced by cutting away thin slices. As seen in Fig. 3, B/A for whole liver is substantially greater than that of homogenized liver or the haemoglobin solution, of the same dry weight.

It should be noted that the reported B/A values for liver homogenate and whole liver were determined at 23°C, while those for whole blood and bovine serum ablumin solutions were determined at 30°C. Although the influence of temperature on B/A for these media is generally unknown, the B/A for water is known to increase only slightly with the increasing temperature and, in particular, by 4% in the temperature range 23 to 30°C (Coppens *et al.*, 1965).

Finally, the excess B/A, *i.e.*, the contribution to the value of B/A due to the presence of the solute, per unit concentra-

tion, has been examined as a function of molecular weight of the solute. The B/A value for solutions of dextrose, and also its polymer dextran, in the molecular weight range from about 10^2 to 10^6 Daltons shows the B/A value to exhibit very little dependence on molecular weight (Law *et al.*, 1981).

CONCLUSION

The B/A values of the various biological media investigated thus far seem to suggest that the non-linearity depends upon the spacing distance between molecular components and the architectural features of the structure, but not upon molecular component size.

The authors acknowledge gratefully the partial support for this research by a grant from the National Science Foundation and by a grant from the National Institutes of Health.

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