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Ultrasonic Hysteresis in Biological Media

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Summary. Non-linear mechanical response of viscoelastic strain responding media to high amplitude stress-strain is examined from a phenomenological point of view and found to lead to results compatible with empirical observations of high intensity ultrasound irradiation of brain, liver, and eye lens tissues. The proposed hysteresis model provides for most of the observed dependencies such as an intensity dependent absorption coefficient, an absorption coefficient increasing linearly with frequency, and a dispersionless velocity of ultrasound in soft tissues (excluding lung). The non-linear compliance of tissues further predicts production of half-harmonic signals even in the absence of cavitation.

Introduction

An acceptable theory describing the propagation of ultrasonic waves through, and the onset and further development of irreversible structural changes occurring in, in vivo mammalian tissues (possibly excepting bone and lung), must involve at least some of the experimental findings, viz., absorption coefficient nearly linearly dependent upon frequency (Dunn et al., 1969), dispersionless velocity (Dunn et al., 1969), threshold intensity-time relationships for lesion formation for brain (Dunn et al., 1975), for lens (Lizzi, 1978), and for liver (Frizzell et al., 1977), acoustic emission attending exposures (Lele, 1977), and possibly others. These findings have emerged during the past approximately 40 years of study by investigators in Europe, North America, Japan, and Australia, and a substantial body of information exists for their confirmation.

The view to be put forth in this paper considers that tissue exposed to ultrasound undergoes local mechanical strain in response to imposed acoustical stress and that the analytic tools developed for studying the mechanical behavior of non-biological solids can be applied to obtain a deeper understanding of ensuing events.

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It has long been known that the stress-strain behavior of tissues deviates from the idealized Hooke's law linear relationship at high stress. Yamada (1970) has compiled a rather complete set of stress-strain curves for nearly all organs and tissues of the human body which shows that, for static conditions, nearly all tissues exhibit a linear region beyond which nonlinear behavior prevails and which can be described by a power function $\sigma = K\varepsilon_i^n$, where σ is the stress, ε_i is the inelastic strain, K is the strength coefficient, and n is a number between 0 and 1 characterizing the shape of the curve. Similar results have been observed for dynamic conditions up to several kilohertz (McElhaney et al., 1969; Ester and McElhaney, 1970). Considering viscoelastic phenomena, Galford and McElhaney (1970) conducted a study on scalp, brain, and dura mater which showed that nonlinear stress-strain behavior also occurs at low megahertz frequency rates of cyclic strain.

For stress-strain behavior in the linear region, energy stored during compression or tension is completely returned to the system upon the relaxation of the imposed strain. Energy is not dissipated and the system is physically conservative. For an applied stress amplitude exceeding the linear region, only a partial recovery of the stored energy by the system occurs upon removal of the external stress, with the energy loss being dissipated as heat. During cyclic strain at amplitudes beyond the linear region, loss of energy occurs attending the relaxation of positive and negative stresses. Losses characterized by a constant loss per cycle of the applied stress lead to a high frequency absorption coefficient which increases linearly with the frequency of the cyclic strain, and may be termed hysteresis. Such an energy dissipation mechanism also yields losses which increase directly with increasing applied stress amplitude. This behavior is manifested by an absorption coefficient which is intensity dependent at high intensities.

Nonlinear stress-strain relationships and hysteresis loss mechanisms have been investigated for a wide range of materials. Litovitz and Lyon (1954) found that measurements in the viscous liquids glycerol and pentachlorobiphenyl above the main relaxation frequencies exhibited a frequency independent absorption loss per wavelength which they concluded were suggestive of a type of hysteresis. They further suggested that a common origin for the hysteresis mechanism in liquids and solids may be the coupling of acoustic energy to thermal energy due to the anharmonicities in lattice structures.

Hysteresis processes have been studied in biological materials in association with fatigue failure of bone. Several investigators have obtained nonlinear stress response curves for various bones from several species (Gaynor-Evans, 1973). Based upon empirical stress-strain relations, fatigue life, expressed as the number of cycles of applied cyclic strain until failure, can be predicted. For example, the logarithm of the applied strain amplitude vs the logarithm of the number of cycles to fatigue fracture yields a straight line over several orders of magnitude (Seireg and Kempke, 1969), similar in nature to that found for many non-biological solid materials.

Basquin (1910) proposed an expression that he termed the "exponential law" (actually a power law) of endurance, viz., the relation $\sigma = \sigma_f N^b$, as an empirical description of fatigue, where σ is the stress amplitude required to cause fatigue failure when applied for N cycles, σ_f is the stress amplitude intercept at one cycle, and b is the best fit exponent based on empirical observations. Subsequent elaboration and refinements have given a broader scope and firmer foundation to these views (Morrow, 1965; Feltner and Beardmore, 1970). It is the purpose of this investigation to apply analyses, which have emerged from studies of cyclic plastic strain and fatigue of solids, to an understanding of the observations following in vivo alteration of tissues by exposure to intense ultrasonic fields.

Analysis

Figure 1 shows the monotonic stress-strain response, typical for a wide range of tissues, exhibiting a region of linear Hookean elasticity describable by the stress being directly proportional to the strain, i.e., $\sigma = E\varepsilon$, and the subsequent nonlinear region for which $\sigma = K\varepsilon_i^n$, where σ and ε_i are, respectively, the stress and inelastic strain, E is the modulus of elasticity, n is the cyclic strain hardening exponent and K is the strength coefficient. Beginning with such a generalized stress-strain relationship, integrating the energy dissipated per cycle, and assuming an energy-dependent criterion for failure, a functional description of tissue mechanical failure, which may be useful for describing ultrasonic lesion threshold behavior, is attempted.

It will be considered that the cyclic stress-strain curve is of the form shown in Fig. 2. Here path 1 is the first quarter cycle, and not different than the monotonic relations of Fig. 1. Path 2 is the subsequent path followed as the tissue is forcibly relaxed by the negative-going applied stress. The closed Paths 2 and 3, then, represent the subsequent positive and negative cyclic variations which continue unaltered until failure occurs. In order to facilitate the following computations, it is considered that energy dissipation is associated only with the

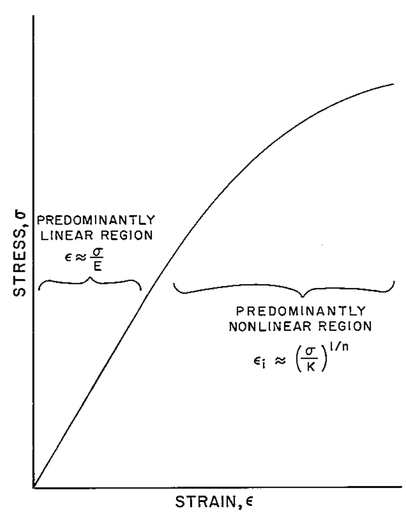

Fig. 1. Mechanical stress vs strain typical of biological materials (Yamada, 1970), exhibiting linear Hooke's law and nonlinear regions

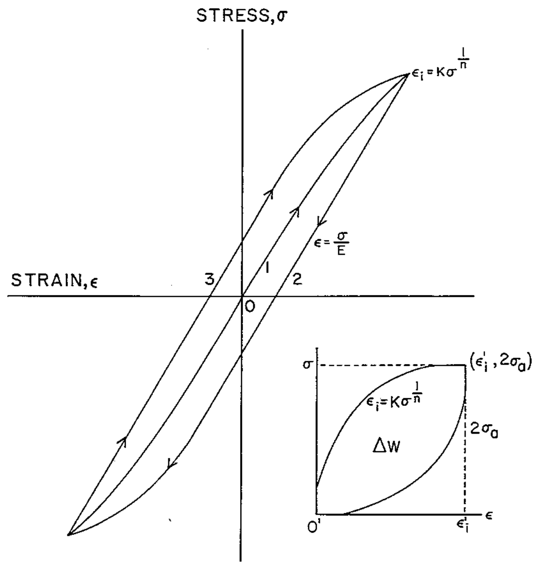

Fig. 2. Cyclic stress-strain curve exhibiting hysteresis. The inset shows only the nonlinear portion and the coordinate system employed in the calculations

nonlinear portion of the stress-strain relationship and that the elastic (linear) portion can be ignored. The insert of Fig. 2 illustrates this procedure wherein the stress and nonlinear strain are represented by a power function and measured from the vertex, O′, of the closed loop, which is also taken as the origin of the coordinate system (Morrow, 1965).

Consider a volume of tissue subjected to a cyclic mechanical strain, as, for example, in the presence of an acoustic wave disturbance. The energy dissipated per cycle ΔW is the integral of the area enclosed by the stress-strain curve, where the elemental energy per unit volume is $dW = \sigma d\varepsilon_i$,

$$\Delta W = \oint dW = \oint \sigma d\varepsilon_i \,.$$

Thus, the area of the closed nonlinear portion of the stress-strain loop is the area of the rectangle enclosing the loop minus the area between the loop and the rectangle, as

$$\Delta W = 2\,\sigma_a \varepsilon_i' - 2 \int_0^{2\sigma_a} \varepsilon_i d\sigma \,. \tag{1}$$

For the nonlinear path described generally as

$$\varepsilon_i = K\sigma^{1/n}\,, \tag{2}$$

the energy dissipated per cycle becomes

$$\Delta W = K\left(\frac{1-n}{1+n}\right)(2\,\sigma_a)^{\frac{1+n}{n}} = 2\,\sigma_a \varepsilon_i \left(\frac{1-n}{1+n}\right). \tag{3}$$

For N identical cycles, the total energy dissipated W_N is

$$W_N = N\Delta W = NK\left(\frac{1-n}{1+n}\right)(2\,\sigma_a)^{\frac{1+n}{n}} = 2\,\sigma_a\varepsilon_i N\left(\frac{1-n}{1+n}\right). \tag{4}$$

It is assumed herein that structural changes are not occurring and that (1) continues to remain valid throughout the process (Feltner and Morrow, 1959). If it is further assumed that failure occurs after a total energy U accumulates at N_f cycles, then

$$U = KN_f\left(\frac{1-n}{1+n}\right)(2\,\sigma_a)^{\frac{1+n}{n}} = 2\,N_f\sigma_a\varepsilon_i\left(\frac{1-n}{1+n}\right). \tag{5}$$

Rearranging gives,

$$\frac{U}{K}\left(\frac{1+n}{1-n}\right) = N_f\,(2\,\sigma_a)^{\frac{1+n}{n}}. \tag{6}$$

Taking the $n/(n+1)$ root and adapting the logarithmic form gives,

$$\log\sigma_a = K - \frac{n}{n+1}\log N_f, \tag{7}$$

where

$$K = \frac{n}{n+1}\log\frac{U(n+1)}{K(1-n)} - \log 2\,.$$

A log-log plot of maximum stress (σ_a) vs number of cycles to failure (N_f) yields a straight line of slope $-n/(n+1)$ and an intercept at one cycle of $\log\sigma_a = K$ (Fig. 3).

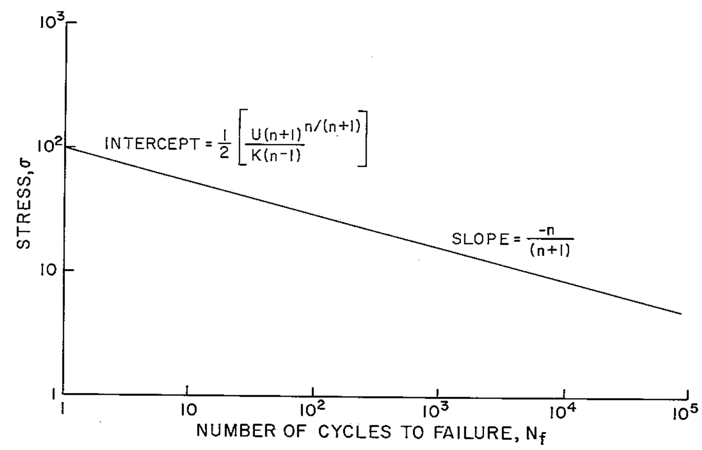

Fig. 3. Stress amplitude for failure vs number of cycles to failure. See (7)

Discussion

Assuming this analysis to be applicable to biological materials, and that energy dissipated as heat by nonlinear stress-strain hysteresis contributes to the heat dissipated by other viscoelastic absorption mechanisms during high intensity ultrasonic irradiation, then (7) may be considered to describe the kinds of events occurring during intense ultrasound exposures leading to irreversible structural changes (Dunn et al., 1975). Assuming plane wave conditions to be extant, the stress amplitude is proportional to the ultrasonic pressure amplitude, and the observed lesion threshold curves can be expressed as a function of the square-root of the delivered acoustic intensity. As time duration and number of cycles are linearly related by multiplying exposure duration by the frequency, the slope of the empirically derived intensity-time plot for lesion threshold (Dunn et al., 1975), which was $-1/2$, would be $-1/4$ on the new plot of pressure amplitude vs number of cycles to threshold. Setting this equal to $-n/n + 1$ in (7) gives an $n = 1/3$, which is consistent with the form of the stress-strain curves found for biological tissues (Yamada, 1970), thus lending credence to the foregoing procedure.

(a) Hysteresis (High) and Low Intensity Behavior

A more generalized formulation could be obtained if the entire hysteresis loop were measurable and the total hysteresis energy dissipation were to be determined as a function of time and stress amplitude. As this is not possible for in vivo biological specimens at ultrasonic frequencies, it may be useful to examine results obtained from the broad range of materials which have been studied, from metals and plastics (Halford, 1966), to elastomers and in vitro biological preparations (Eirich and Smith, 1972). In spite of the wide diversity of materials studied, a common mode of energy dissipation seems to exist for all due to hysteresis type processes. It emerges that on a log-log plot of strain amplitude vs number of cycles required for mechanical failure, two distinct regions appear. For high amplitude strain imposed for short durations, a region of so-called low cycle fatigue predominates and, as the description above implies, the applied strain forces the materials well into non-linear behavior. At lesser amplitude levels, a transition to predominately elastic strain occurs as non-linear hysteresis behavior becomes less significant and the slope of the log-log plot becomes a fraction of its value at high amplitude strain. (An additional phenomenon exists at even lesser strain levels, wherein heat is dissipated as it is produced, and a level is reached below which no mechanical failure is observed, even for very prolonged periods of cyclic stressing.)

These two major regions of interest have been found empirically to be describable by the sum of the elastic $\left(\varepsilon_e = \dfrac{\sigma_f}{E} N_f^b = \dfrac{\sigma_f}{\sigma_a} N_f^b\right)$ and inelastic ($\varepsilon_i = \varepsilon_f N_f^c$) strain terms (Morrow, 1965), shown in Fig. 4, as

$$\varepsilon = \frac{\sigma_f}{E} N_f^b + \varepsilon_f N_f^c \tag{8}$$

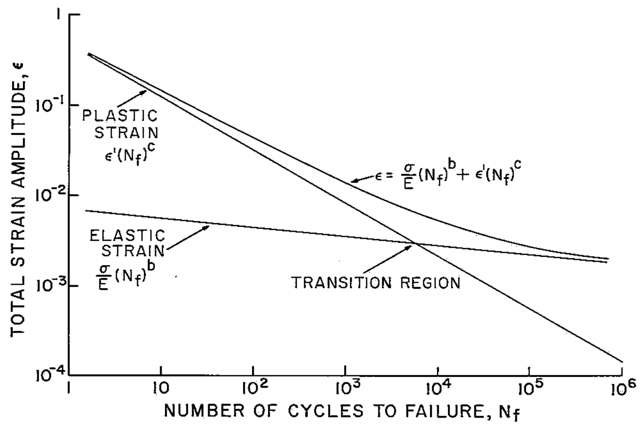

Fig. 4. Plastic and elastic strain vs number of cycles to failure

where, for metals at least, b is the strength exponent, c is the ductility exponent, ε_f is the ductility coefficient, and σ_f is the strength coefficient. These parameters may be approximated from independent physical measurement. As N_f, the number of stress cycles to failure, is related to both stress and strain, it follows that b and c are not independent. The ratio of b to c is the value of the exponent n, describing the power function fit to the non-linear region of the stress vs strain plot in Fig. 1, and (1), as seen from

$$N_f = \left(\frac{\varepsilon_i}{\varepsilon_f}\right)^{1/c} = \left(\frac{\sigma_a}{\sigma_f}\right)^{1/b},$$

from which $b/c = n$.

Additional considerations fix the values of the exponents b and c. The total energy dissipated (U) by cyclic hysteresis up to the threshold of tissue structural failure using the component terms of (8) and (5), is given by (Halford, 1966)

$$U = 2\,K\left(\frac{1-n}{1+n}\right)\sigma_f\varepsilon_f N_f^{1+b+c}\,. \tag{9}$$

The empirical finding (Johnston and Dunn, 1976), that the threshold relation for production of irreversible, structural changes in mammalian brain is $It^{1/2} = 200$ (I is the ultrasonic intensity at the site of the lesion and t is the length of the exposure), can be rewritten in terms of the acoustic stress (square-root of intensity) and the number of cycles to threshold N_f (directly proportional to exposure duration t) as

$$N_f \approx \sigma^{-4}\,. \tag{10}$$

Using (10) with (6) yields, since $U \sim N_f\sigma^{\frac{1+n}{n}}$ and $U \sim \sigma^{-4}$

$$N_f = \frac{\left(\frac{\sigma_a}{\sigma_f}\right)^{-4}}{\left(\frac{\sigma_a}{\sigma_f}\right)^{\frac{1+n}{n}}} = \left(\frac{\sigma_a}{\sigma_f}\right)^{\frac{-(1+5n)}{n}} . \tag{11}$$

Thus

$$b = -\frac{n}{1+5n}, \tag{12}$$

and

$$c = -\frac{1}{1+5n} . \tag{13}$$

It is interesting to apply these relationships to experimental data for lesion production in various tissues by exposure to high intensity ultrasound. For example, Lizzi et al. (1978) report that the threshold of production of cataracts in rabbit eye lens, in the range of 200 to 2,000 W/sq cm, exhibits two distinct regions on a log-log plot of intensity vs exposure time. At high intensities, 600 to 2,000 W/sq cm, the slope of the line on the plot is -1. Values obtained from their reports at intensities of 400 W/sq cm and less exhibit a second region for which the slope of the curve has decreased to approximately -0.23. When the relationships in equations 8, 12, and 13 are used, slopes of -1.0, at the high intensity levels, and -0.20, at transition levels and below are obtained when a value of $n = 1/5$ is used.

For brain tissues, the slope of the threshold line on a log-log plot of intensity vs time is widely found to be $-1/2$ (Dunn et al., 1975) at exposure levels of 100 to 10,000 W/sq cm. For low level irradiations of 50 to 15 W/sq cm, there is a decrease in slope to approximately -0.25 (Johnston, 1979). Calculated values for the slopes using (8), (12), and (13) yield slopes of -0.50 and -0.30.

Similar agreement is obtained for liver, kidney, and testicle irradiation data as given by Frizzell et al. (1977). At levels near a 1,000 W/sq cm and above, a slope of $-1/2$ is observed. Although less data exists below 500 W/sq cm, a definite decrease in slope is observed as irradiation intensities are reduced below this level. Irradiations at 1, 5, 10, and 50 s yield an approximate slope between -0.25 and -0.30.

Figure 5 shows the delivered intensity vs pulse duration for the above mentioned tissues and the dashed lines are predicted by (8). Although the slopes may be derived from the equation, the absolute intensity levels for the thresholds are not obtainable from purely mechanical stress-strain hysteresis considerations. Physiological considerations in in vivo tissues, including ultrasound absorption coefficient differences, must also enter into threshold lesion production as summarized in Table 1. The similar mechanical properties of the soft tissues brain, liver, kidney, and testicle all yield similar slopes for high and low level irradiation. However, the intensity levels required to produce a

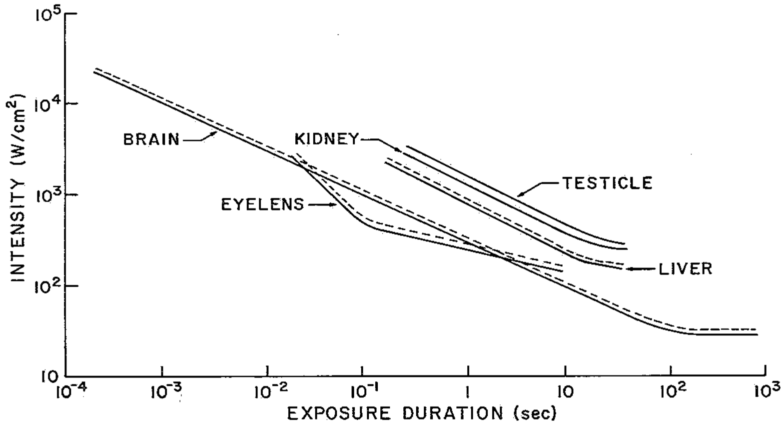

Fig. 5. Ultrasonic intensity vs exposure duration for threshold lesion production in brain (Dunn et al., 1975), eye lens (Lizzi et al., 1978), and liver, kidney and testicle (Frizzell et al., 1977). The dashed lines are predicted by (7)

Table 1

Tissue	Perfusion	Observed slopes	Intercept (l/s)	n
Lens		-1 to -0.23	300	1/5
Brain	Blood vasculature	$-1/2$ to -0.25	200	3/5
Liver	Blood vasculature and biliary duct system portal veins	$-1/2$	500	3/5

lesion are quite different due to differences in the absorption coefficient. As the absorption coefficient decreases from that of brain to that of testicle, the required lesion threshold intensity increases. Additional physiological differences are due to each tissue's blood flow perfusion characteristics and homeothermic response to increases in temperature. This is seen in its extreme by the dramatic differences between liver tissue, which is highly vascularized, and eye lens tissue, which has no blood perfusion. The additional mechanical differences of eye lens tissue, which is a polycrystalline solid, and that of soft tissue, further enhance the lesion threshold behavior.

(b) Harmonics Production

When a system is driven into a region of nonlinear behavior, the frequency domain description requires that harmonics be produced at integer multiples of the fundamental driving frequency. An acoustic phenomenon in liquid media is the generation of sub-harmonics, in particular at one-half the fundamental driving frequency resulting from small bubbles, in the fluid medium, being driven at twice their resonant frequency (Eller and Flynn, 1969). This phenomenon also exhibits a definite intensity threshold and can be used as a monitor for the detection of cavitation threshold (Eller and Flynn, 1969). Lele (1977) has performed similar measurements at megahertz frequencies in water, brain, and liver and found the presence of half harmonic signals at levels well below the threshold for collapse cavitation, down to levels of a few tenths of a Watt per square centimeter. There appeared to be a transition region at the level of collapse cavitation above 1,500 W/sq cm where the amplitude of the sub-harmonic increased rapidly, though no threshold for the half-harmonic was seen at low intensities. Neppiras (1969) noted that it had been observed that half-harmonic signals could occur in the absence of bubbles and cited the work of Tucker (1965) and G. J. Dunn et al. (1965). These investigators had found that strong half-harmonic signals could be generated due to the nonlinear compliance of the medium and that the presence of bubbles was not always necessary for the observation of half-harmonic signals. They stated, additionally, that the nonlinear compliance of the system would explain only the half-harmonic signals. Thus, hysteresis in tissues due to nonlinear stress-strain may be responsible for the signals at one half the driving frequency.

(c) Velocity Dispersion

Hysteresis, as proposed by Mason and McSkimmin (1974) for metals and glasses, and the mathematical development for it proposed by Mason (1950), yielded a frequency independent value for velocity. Although Mason and McSkimmin (1947) and Litovitz and Lyon (1954) conducted hysteresis absorption studies in metals, glasses, and viscous liquids, velocity data was never obtained. Measurable velocity dispersion has not been observed in most biological soft tissues (Goss et al., 1978, 1980), though dispersion in non-homogeneous tissues such as lung (Dunn, 1974) and bone (Yoon and Katz, 1976) is known to occur.

Care must be taken in dispersion measurements in tissues to exclude group-velocity dispersion due to frequency-dependent boundary impedances which may interfere with velocity measurements, as demonstrated by Lange (1966). Further, the measurement of a frequency dependent variation in velocity which would contradict the dispersion-free velocity prediction of the hysteresis model may have to be conducted at intensity levels where hysteresis is proposed to predominate as a nonlinear effect (several hundred Watts per square centimeter).

Summary

It has been shown that a multiplicity of physical behaviors are determined by the single constant n, the exponent of the power curve fit to the nonlinear stress-strain behavior of tissues. The value of n is found to be consistent with observed stress-strain nonlinearities and to yield slope data consistent with empirical lesion threshold data at high intensity levels, and at transition levels to low intensity behavior. The ability of the phenomenological theory to satisfy several physical constraints by a single variable suggests the utility, if not the validity, of such a hysteresis model.

Additional verification could be sought by experimental examination of harmonic production and velocity dispersion in tissues. However, in the absence of specific experiments, sufficient data now exist showing half-harmonic production without cavitation and extensive literature searches (Goss et al., 1978, 1980) show no velocity dispersion in soft homogeneous tissues.

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