Nonlinearities in the Bioeffects of Ultrasound

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Abstract: Biological effects of ultrasound involve nonlinear phenomena in qualitatively different ways. (1) The propagation of sound itself is nonlinear. Most nonthermal bioeffects of interest to users of diagnostic ultrasound require acoustic pressures great enough that the wave becomes distorted by nonlinear propagation. Under limiting conditions this process can increase the absorption parameter of weakly absorbing media by orders of magnitude. (2) Acoustic cavitation is highly nonlinear. At low amplitudes the response of a bubble is dominated by the acoustic pressure. At a critical acoustic pressure, however, the inertia of the surrounding medium becomes controlling. At this threshold, a 10 or 20% increase in acoustic pressure leads to increases in the collapse pressures in the bubble by orders of magnitude. (3) Very little of the biochemistry, physiology and pathology of the biological system is linear. The rates of biochemical processes, including thermal denaturation of biological macromolecules, are exponential functions of the temperature. Whether the physical process of heating by ultrasound is linear or nonlinear, this leads to a very strong nonlinear dependence of thermal tissue damage and teratological effects upon the levels of ultrasound.

INTRODUCTION

Until the early 1980s, the development of medical ultrasound proceeded under the tacit assumption that sound propagation is linear. Today, we realize that the effects of nonlinear propagation can be seen in almost every medical use of ultrasound. Mechanisms that produce biological effects, such as cavitation, and the biochemical reactions of the molecular components of tissue to the heat generated by ultrasound are themselves highly nonlinear.

NONLINEAR PROPAGATION

The equipment used for diagnostic ultrasound typically operates at frequencies from 2 to 10 MHz, at tissue depths greater than 10 cm and at negative pressures up to approximately 4 MPa. It is necessary to specify negative pressure rather than pressure amplitude because, at those levels, frequencies and propagation distances, nonlinear propagation, defraction and dispersion produce a distorted waveform which typically is characterized by a sharp spike of positive pressure and a relatively slowly changing negative phase.

For small signals, tissue losses are well characterized by their absorption coefficients. In that case, the absorption coefficient is found to depend only upon the frequency dependent characteristics of the propagating medium. For the finite amplitude ultrasonic waves frequently used in medicine, the absorption process depends upon the source amplitude, geometry of the sound field, the distance traveled and the nonlinear properties of the medium, as well as on frequency. This finite amplitude absorption is completely foreign to the familiar loss mechanisms that characterize linear propagation. Finite amplitude losses occur only when a pressure discontinuity has developed in the wave front and depend upon the degree of shock formation. These finite amplitude losses are essentially independent of the magnitude of the linear absorption coefficient of the medium as long as the linear losses are small. Under appropriate conditions, the effective absorption parameter of water, for example, can be enhanced by two orders of magnitude and can become as large as the linear absorption coefficients of some of the soft tissues of the body (1). These nonlinear contributions to heating are most pronounced in sharply focused sound fields.

Christopher's model (2) illustrates the effects of nonlinear propagation on acoustic fields in tissues and water (Figure 1) and on heating rates (Figure 2) in a typical application of diagnostic ultrasound. Note that qualitatively similar effects occur in water and in liver tissue. Saturation takes place in both media but higher source intensities are required in liver because its relatively large linear absorption inhibits shock formation. The axial heating rate at the focus in liver is nearly doubled as shock formation gets underway but the steady state focal temperature is only modestly affected because the narrower heating pattern under those conditions increases thermal diffusion.
The dramatic increase in the absorption parameter of water results in a significant increase in the transfer of momentum from the sound beam to the fluid. The enhanced radiation force on the water increases streaming.

![Graph showing Focal Intensities. 3 MHz, 1 cm radius source, 8 cm focal length. Dotted lines are linear extrapolations. Adapted from (2).](image1)

**FIGURE 1.** Focal Intensities. 3 MHz, 1 cm radius source, 8 cm focal length. Dotted lines are linear extrapolations. Adapted from (2).

**FIGURE 2.** Normalized Focal Heating Rates for Source in Figure 1. Liver (solid line), Fat (dotted line). Adapted from (2).

**CAVITATION**

By driving bubbles with sound near their resonance frequencies, large amplitudes of motion can be achieved. Steady oscillations of bubbles in a sound field create local stresses in neighboring cells that can result in movement of intercellular contents or in rupture of their membranes if the amplitudes of motion are sufficiently great. At frequencies of 1 or 2 MHz, as the pressure amplitude increases the bubbles respond at first linearly but, when the amplitude of oscillation is comparable to the equilibrium size of the bubble, the inertia of the surrounding medium dominates the collapse of the bubble giving rise to internal pressures which are orders of magnitude greater than the acoustic pressures driving the phenomenon (3). At about that level, a small increase in acoustic pressure amplitude can lead to orders of magnitude increase in the collapse pressure within the bubble. The transition to inertial dominance is abrupt leading to the concept of a threshold pressure for inertial cavitation. The threshold for inertial cavitation increases with frequency. Thus, the sharp positive pressure spikes that arise during shock formation at high amplitudes have little effect on cavitation. Instead, the fundamental pressure or negative pressure in a nonlinearly distorted pulse should be used as predictors of inertial cavitation.

**BIOCHEMICAL RESPONSE**

The rate at which thermal damage is produced by heat is an exponential function of the activation energy of the denaturation of the molecular components of tissue and the absolute temperature (4). Thus, lesion production and teratological effects are highly nonlinear regardless of the physical mechanisms by which ultrasound produces heat.

**ACKNOWLEDGMENTS**

Much of the research reported here has been supported by grants from the National Institutes of Health and the Whitaker Foundation.

**REFERENCES**