Ultrasound Bioeffects and Regulatory Issues: An Introduction for the Echocardiographer

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Echocardiography is one of the most widely used methods of evaluating diseases of the heart and circulation in adults, children, infants, and fetuses. Many factors are responsible for the extraordinary acceptance of echocardiography throughout the world. Among these factors are the diagnostic efficacy of the method, the relatively low cost of ultrasound imaging equipment (compared with other modalities), the compact size and thus portability of the instrumentation, and the noninvasive nature of the procedure. In addition, an extremely important factor leading to the continued use of echocardiography, particularly in infants and fetuses, is its extraordinarily good safety record. Echocardiography has been in common clinical use for two decades, and during this time there has been no documented evidence of any kind that harm results from clinical examinations. Thus echocardiographers and sonographers commonly consider ultrasound examinations to be without substantial biohazards.

Against this backdrop of apparent safety, as defined by widespread clinical experience, it may have come as a surprise to many practitioners to learn of a growing controversy concerning proposed additional regulation of ultrasound imaging equipment as a result of the question of potentially harmful bioeffects from ultrasound. Through its application surgically, it is well known that high-intensity ultrasound causes damage to biologic tissues; this has been recognized from the earliest experiences with underwater sound ranging.[1] Evidence of bioeffects of ultrasound in vitro and in vivo has more recently been documented under better controlled dosimetric conditions.[2] Evidence of adverse biologic effects to humans from ultrasound as used in diagnostic clinical echocardiographic instruments, however, has yet to be demonstrated. Nonetheless, substantial recent activity by regulatory agencies has raised concern among manufacturers, practitioners, and patients.[3] What is the basis for this concern? What are the relevant observations, both experimental and clinical, which support the safety versus potential hazards of diagnostic ultrasound? In an attempt to answer questions such as these, the Physics and Instrumentation Committee of the American Society of Echocardiography has prepared this educational document concerning ultrasound bioeffects and echocardiography. In this article we present (1) definitions of some of the physical measurements utilized to characterize the acoustic output of ultrasound instruments; (2) definitions of bioeffects that have been demonstrated in experimental studies (including what is known or speculated concerning their mechanisms); (3) a brief, selective overview of the literature on bioeffects, including in vitro and in vivo data; and (4) an overview of some of the regulatory issues and processes that affect the manufacture and use of ultrasound imaging systems. Our overall goal is to introduce these concepts to echocardiographers and sonographers so that they may more knowledgeably interpret the increasing amount of information likely to appear in the professional and lay media concerning potential bioeffects of diagnostic ultrasound.

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BASIC CONCEPTS RELEVANT TO THE LITERATURE ON ULTRASOUND BIOEFFECTS

Acoustic Output Definitions

An appreciation of the magnitude of the ultrasonic energy emitted from a transducer is important in the

selection and prudent use of diagnostic equipment. Following is a list of some terms that are useful for characterizing acoustic emissions in diagnostic ultrasound.[4]

Pressure. The transducer launches a pressure wave into the tissues. The propagating pressure pulse causes regions of rarefaction and compression within the tissue. Pressure is defined as a force per unit area and is expressed in units of atmospheres or pascals.

Energy. Energy is the capacity to perform work (for example, the capacity to raise the temperature of a tissue) and is usually measured in joules. In ultrasound the energy associated with the propagating pressure wave is the sum of the kinetic energy of the particle velocity of the tissue and the potential or stored energy in the compressed or rarefied regions of the propagating wave.

Power. Power is defined as the rate of doing work (that is, the rate at which energy is introduced into a tissue) and is usually measured in watts (joules per second). If the power delivered to a tissue is doubled, the temperature will rise twice as rapidly.

Intensity. Intensity is the most commonly quoted ultrasound emission measurement. Intensity is the power per unit area and is usually measured in watts per square centimeter. It is related to the square of the pressure amplitude and is always a positive quantity. Over the past few years a variety of specific intensity measurements has been developed for use with medical ultrasonic instrumentation.[5]

Temporal average intensity (I_{ta}). The pressure and intensity observed at a particular point in a tissue vary with time (Figure 1). Temporal average intensity is the intensity averaged over one pulse repetition period.

Spatial average temporal average intensity (I_{sata}). Intensity at a point also varies with the position of the point with respect to the beam axis (for example, off-axis intensity is lower than on-axis intensity). Spatial average temporal average intensity is the temporal average intensity averaged over the cross-sectional area of the beam.

Pulse average intensity (I_{pa}). The intensity averaged over the pulse duration instead of over the pulse repetition period (Figure 1).

Spatial average pulse average intensity (I_{sapa}). The pulse average intensity averaged over the beam cross-sectional area.

Spatial peak refers to the position in the acoustic field where an intensity variable is at a maximum value.

Spatial peak pulse average intensity (I_{sppa}). The pulse average intensity at the spatial point where the pulse average intensity is at a maximum value.

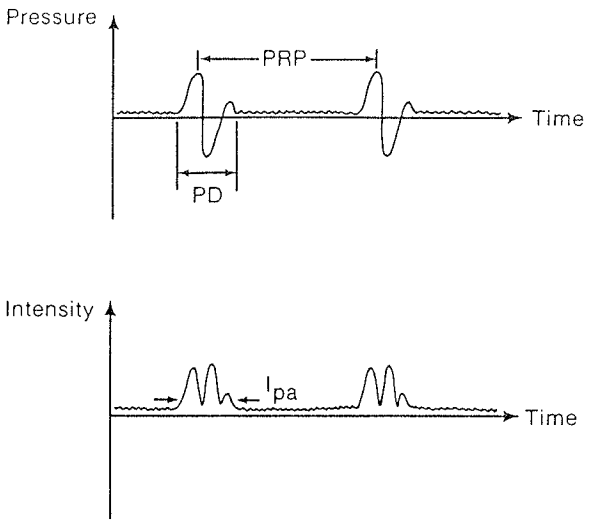

Figure 1 Ultrasound pressure and intensity waveforms. Top shows pressure observed over time at fixed spatial position. Propagating pulse has pulse duration, *PD*, and recurs with pulse repetition period, *PRP*. Bottom shows corresponding intensity waveform. I_{pa}, Intensity averaged over pulse duration.

Spatial peak temporal average intensity (I_{spta}). The value of the temporal average intensity at the spatial point in the acoustic field where the temporal average intensity is at a maximum value.

Bioeffects: Definitions and Mechanisms

There are several mechanisms by which ultrasound may potentially interact with and affect biologic systems.[6-8] These mechanisms include (1) thermal mechanisms by which tissue temperature is elevated by interaction with ultrasound, (2) cavitation mechanisms by which gas-filled bodies or bubbles are either created by ultrasound or made to vibrate in a destructive manner by ultrasound, and (3) other mechanisms not including the former two but including such effects as radiation forces, acoustic streaming, and microstreaming. In the following sections we define some equations relating to these mechanisms and describe, when appropriate, what is understood about the various mechanisms.

Thermal mechanisms. The best understood mechanism is the effect of increased temperature on biologic systems; there is a vast literature concerning the effect of increased temperature on molecules, cells, tissues, and organ systems. We begin in this section to describe the relationships between some measurable parameters: intensity (I), depth into the tissues (x), and temperature (T) of the tissue. Thus we attempt to obtain relationships between extrinsic variables that can be measured externally, especially

temperature, and intrinsic variables of the tissues such as density, speed of sound, or specific heat.

Equation 1 describes the propagation of a plane ultrasound wave into a homogeneous tissue.

$$I = I_o \exp(-2Ax) \qquad \text{Eq. 1}$$

In the equation, A is the amplitude attenuation coefficient and is a characteristic of a particular tissue. Attenuation or decrease in signal amplitude as the wave passes through tissue is caused by both absorption and scattering of sound by the tissue. I_o is the intensity at the point in the tissue at which x equals zero. One can see from this equation that the intensity decreases with x fairly quickly, depending on the value of the attenuation coefficient, A. One must remember, however, that this equation is for a plane wave. In most clinical systems the wave is not planar but focused. Therefore the propagating wave equation is more complex, and the intensity may actually increase with depth into the tissue if focusing effects predominate over attenuation effects. The relationship between this equation and changes in temperature is described by equation 2.

$$\frac{dT}{dt} = 2\frac{\alpha I}{\rho c_m} \qquad \text{Eq. 2}$$

where $\frac{dT}{dt}$ is the rate of increase in temperature, α is the absorption coefficient, t is time, ρ is the mass density, I is intensity, and c_m is the specific heat of the tissue. A in equation 1 is the attenuation coefficient, whereas α in equation 2 is the absorption coefficient. Equation 2 states that the temperature increases at a rate proportional to the intensity and the absorption and inversely proportional to the density and specific heat. The greater the intensity, the higher the delivery of heat to the region for a given absorption. If the exposure of intensity to the region is fixed and the absorption increased, however, more heat is produced from the ultrasound passing through the region, and therefore the temperature increases more quickly. The effect of density and specific heat in this equation is such that relatively dense tissue such as muscle will not heat quite as quickly as less dense tissue such as fat. To illustrate how rapidly temperature would increase in a biologic material, given typical measurements, let us assume that density is 1 gm/ml (the density of water) and that the tissue specific heat is 1 calorie/gm/° C (about the same as for water). Assuming $\alpha = 0.05$/cm (which is approximately correct for liver at 3 MHz) and assuming that intensity is 1 W/cm^2, a value for $\frac{dT}{dt}$ of 0.024° C/sec or 1.44° C/min is obtained. Most diagnostic systems do not expose tissues to such high energy continuously; however, during the short period of exposure the temperature would rise at about this rate. Perfusion of tissue by blood has a cooling effect and tends to offset temperature increases caused by exposure to ultrasound. There are some reviews in the literature concerning absorption of ultrasound[8-11] and there is a compilation of characteristics of tissue measurements by Goss et al.[12] A more extensive review of experimental physics in ultrasound can be found elsewhere.[11,13] The fundamental mechanisms of ultrasound absorption are not well understood in biologic tissues, except that in general, absorption is primarily related to the concentration of proteins and other large molecules and is secondarily related to the secondary and tertiary structures of proteins.[14]

There is another mechanism that is related to loss of energy, and that is scattering. Although considered a small part of attenuation relative to that caused by absorption, scattering can enhance heating by redirecting the acoustic energy into a more confined region, thus increasing intensity. Therefore in some sound propagation modes, heat can be generated at tissue inhomogeneities. This has been found to be true in lung tissue and may occur in other relatively inhomogeneous tissues.

Heat diffusion is not emphasized in the above description. Temperature distributions caused by ultrasound are functions of time and space, depending on a wide range of intrinsic and extrinsic factors. The extrinsic factors are the shape of the impinging field and its intensity; the intrinsic factors are the spatial distribution of scattering and absorption coefficients, density, specific heat ratio, perfusion rate, and heat conduction. The mechanisms by which heat may be physically carried from a tissue region, such as with blood flow or fluid flow, are termed *convection mechanisms,* whereas those associated with heat flow itself through the material are termed *conduction mechanisms*. Convection mechanisms are important in live tissue because of blood flow.[8]

Cavitation. By cavitation we mean an ultrasonically induced activity of highly compressible bodies of gas, bubbles, or cavities.[15] These small bubbles vibrate, sometimes violently, in association with ultrasonic exposure. Sometimes the oscillations can be simple, that is, symmetric and therefore predictable in nature, or they can be quite complex and violent. A bubble can become a secondary source of sound and therefore can exert forces on objects in its immediate environment through such effects as radiation pressure, streaming, or torque production.

Resonance of bubbles. As a microbubble is exposed to a sound field, it increases and decreases in radius, depending on its diameter in relationship to the frequency of sound. At very low frequencies the pressure is in phase with the pressure in the bubble, and therefore the radius has a maximum value when the applied pressure is minimal and vice versa. Because the bubble changes size by moving a mass of material outside its surface, however, one can imagine that there is a limit or at least a resistance to completely free motion of the bubble. Therefore at very high frequencies the applied pressure and the pressure in the bubble can be out of phase, thus the volume can be increasing while the applied pressure is increasing. At a certain point these can be 180 degrees out of phase, resulting in a form of resonance; thus the gas within a sphere acts as a spring, whereas the liquid just outside a sphere acts as a mass, and a spring masslike resonance results. The resonance frequency can be given by equation 3.

$$F_o = \frac{3260}{R_o} \qquad \text{Eq. 3}$$

where F_o is frequency in kilohertz and R_o is radius in microns. Therefore a bubble 100 μm in radius is resonant at 32.6 kHz in water.[16] This relationship breaks down at high frequencies in bubbles resonating in the megahertz range. Under resonant conditions, violent oscillations can occur, resulting in a wide range of effects such as streaming, shearing, and creation of torque within the associated liquid.

Sound absorption by bubbles. As a consequence of vibration, the bubble can absorb energy from the sound field. Some of this energy will be converted into heat, and some will be reradiated from the bubble as a spherical sound wave. In water a bubble resonating at 1 MHz in a field having an intensity of 100 mW/cm^2 can take 60 μW from the field, and about 90% of this is converted to heat.[17] If biologic tissue in a region contains distributions of such bubbles, it might absorb sound readily, acting as a good heat source with the mechanisms described in the previous section. Thus heating may be expected to occur exponentially in tissues that may have distributions of bubbles that are of a size near the resonance of the insonifying sound.

Rectified diffusion. An unusual aspect of the behavior of small gas bubbles in liquid is that they can grow in a sound field.[8] This growth is associated with the diffusion of gas through the liquid surrounding the bubble. Oscillation of the bubble causes gas to diffuse inward and outward during each cycle because of the variations of pressure within the bubble. The diffusion inward and outward, however, can be asymmetric so that the bubble grows, since the sonically produced inward flow exceeds the outward diffusion flow. This phenomenon is termed *rectified diffusion* and is important in the study of the dynamics of sonic cavitation. Only tiny bubbles are resonant at high frequencies. Tiny bubbles have small radii of curvature and therefore tend to collapse because of surface tension. Under insonification by ultrasound, however, rectified diffusion can aid in the cavitation process, preventing bubbles from shrinking. Therefore an undesirable occurrence actually may take place; that is, bubbles that are too small for resonance may grow to the size of resonance and absorb a great deal of energy. For bubbles of certain sizes to be produced or maintained by rectified diffusion, however, the sound level must exceed some threshold.

Microstreaming near pulsating bubbles. One can imagine that if a bubble is pulsating in an asymmetric manner, the pulsation of the bubble could produce eddies or shear waves in the immediate adjoining liquid. This motion is typically termed *microstreaming*. If the air bubble or pocket is at a surface or at some other air space between materials of differing acoustic characteristics, high velocity gradients can be obtained on the boundary.[15,18] For instance, large molecules in these regions can be subjected to regions of high velocity gradients and therefore to a shearing action that may cause damage, such as fragmentation.

Cavitation nuclei. We have been discussing the effects of bubbles already present in the tissue. Ultrasound can also create bubbles at sufficiently high intensities. The creation of bubbles requires cavitation nuclei either as small bubbles or other sources of nucleated gas or vapor for cavitation to begin. One source of these cavitation nuclei is gas trapped in cracks or corners of small particles. Under these conditions the radius of curvature of the surface of the bubble is small, and therefore the pressure within the bubble can be low so that it will not dissolve in the fluid. Whether this occurs in fluid or soft tissues is unknown. Another mechanism for stabilizing gas nuclei has been proposed by Fox and Herzfeld,[19] in which organic molecules can collect on the air-liquid interface of a bubble and decrease the diffusion of the vapor or gas from the interior of the bubble out into the liquid by stabilizing the bubble against the solution.

Overview of acoustic cavitation. Typical diagnostic systems can produce powers of the order of 10 to 100 W for a few cycles. This represents peaks of 5 to 15 atm of pressure for a few cycles. It has been shown that the so-called viscous start-up time for a bubble in water is small compared with an acoustic period and that bubbles with initial radii less than

about 3 μm are not inertially limited, implying that significant bubble growth could occur in water to a maximum size of about 7 to 7.5 μm. The pressure of a bubble that starts at 3 μm and goes to 7 μm and collapses to a minimum size of less than 1 μm can be greater than 200 atm. The internal temperature could reach approximately 1000° C. This would give an energy density of about 100 J/cm^3.[15] Although these are crude estimates, they demonstrate the order of magnitude of energy concentration that can be caused by cavitation in water. In tissues, however, the effective viscosity is many times greater than in water, and therefore bubble motion is greatly limited. In addition, little attenuation is required to decrease greatly the intensities of diagnostic units.

Other mechanisms. There are many other mechanisms of possible importance in ultrasound bioeffects that are not based on thermal or acoustic cavitation processes. However, the relationship of these mechanisms to actual biologic effects at diagnostic intensity levels associated with echocardiographic equipment is unclear. These various mechanisms are acoustic boundary layer, acoustic microscopic streaming, effects of viscous stresses, radiation force, and radiation torques.

A great deal of investigation has been accomplished in a microstreaming situation in which a cylinder is vibrated transversely with respect to its axis. This results in microstreaming about the tip of the cylinder and has been used for a wide range of biologic effects studies.[20,21]

Stresses occur when velocity gradients are found because of either microstreaming or alterations in acoustic characteristics of the tissue within which the field is propagating. One can imagine that micromolecules caught in a stream either flowing or oscillating, in which the velocities vary strongly as a function of space, can be subjected to a great deal of shear stress and perhaps be altered.

Summary

The effects of ultrasonic energy on tissue can be divided into three main mechanisms: thermal, cavitation, and other mechanisms. Thermal effects are those associated with a rise in temperature, and its associated effects on molecules and cells are fairly well known. Cavitation effects are far more complex, and although they occur with lower probability in biologic tissues than in aqueous systems, they can be more serious than thermal effects. Even if the required bubbles or nucleation occur in tissues, the effects of absorption and viscosity will greatly moderate the possibilities of cavitation effects. The other mechanisms, such as radiation pressure and radiation streaming, may even have lower probability of occurring in tissue.

BIOEFFECTS LITERATURE: AN OVERVIEW

From the earliest uses of ultrasound for underwater ranging, biologic effects of high intensity ultrasound have been evident.[1] Thus, as has been emphasized by O'Brien,[22] during the entire development of medical ultrasound applications, both diagnostic and therapeutic, significant attention has been paid to the possibility of adverse biologic consequences of this energy form. Because ultrasound has been used for medical applications for over 20 years, it is not surprising that a voluminous amount of literature regarding bioeffects of ultrasound has accumulated. The literature may be considered within four categories: (1) in vitro studies of mechanisms potentially relevant to in vivo bioeffects (these studies commonly utilize aqueous solutions or preparations of cells), (2) in vivo studies utilizing animal models, (3) epidemiologic analyses of clinical experiences, and (4) review of various aspects of the literature. Because the present article is intended to be an introduction to the field of ultrasound bioeffects, no attempt has been made to again exhaustively review the extensive literature in this area. Instead, we have attempted to identify the general trends of studies and, most importantly, current areas of controversy and/or investigative interest in this field. The interested reader is referred to several of the many excellent reviews on the subject[2,7,22-35]; original research sources are not extensively referenced in this article.

General Comments on the Bioeffects Literature

Although the experimental design, ultrasound exposure conditions, and other details of the many studies of ultrasound bioeffects vary widely, some general statements regarding the literature may be made at the outset. First, as opposed to the x-ray bioeffects literature, no generally accepted measure of absorbed ultrasound energy is available. Thus the emitted ultrasound energy is the value that is often quantified in experiments relating to ultrasound bioeffects. As discussed above, several ultrasound acoustic output variables may be quantified; virtually all of these have been defined under so-called free-field conditions in which ultrasound emission is mea-

Table 1 Summary of the maximum ultrasonic output quantities for diagnostic ultrasonic equipment

Equipment type	W (mW)	I_{spta} (mW/cm²)	I_{sppa} (W/cm²)	I_m (W/cm²)	p +/− (atm)
Manual compound scanners	20	200	300	700	50
M-mode	75	225	700	300	30
Autosector scanners	50	30	200	250	30
Sequential Linear Array Scanners	55	10	200	100	20
CW Doppler, obstetrics	40	80			
Pulsed Doppler, cardiac	70	1900	100		
Pulsed Doppler, peripheral vascular	10	700	12		

From O'Brien WD. Echocardiography 1986;3:165-79.
W, Ultrasonic power; I_{spta}, spatial peak temporal average intensity; I_{sppa}, spatial peak pulse average intensity; I_m, maximum intensity; p +/−, maximum or minimum ultrasonic pressures; CW, continuous wave.

sured in water or a similar medium. Because of the effects of ultrasound absorption, reflection, and diffuse scattering in biologic tissue, these free-field exposure conditions no doubt differ from those to which particular organs are actualy exposed in vivo. One therefore must be aware of the difficulty in quantifying specific exposure conditions and thus comparing sometimes quite disparate experimental results. A second consideration is that some of the currently available data in the bioeffects literature were obtained utilizing broad-beam, therapeutic devices or other systems not necessarily similar or relevant to currently used, focused, pulsed ultrasound diagnostic imaging systems. Thus in reviewing particular studies in this area one must be aware of the type of ultrasound emission system utilized in the study and its relevance to modern diagnostic pulsed and continuous wave systems. A third and final general point to be emphasized is the multiplicity of purposes that ultrasound has in medicine. Although echocardiographers are concerned exclusively with diagnostic uses of ultrasound in imaging and Doppler applications, there is a widespread and growing interest in therapeutic and surgical uses of ultrasound. Naturally, bioeffects are expected and desirable in the therapeutic and/or surgical uses of ultrasound; thus one must be cognizant of the intent and hypothesis of a particular study in interpreting its results. Ultrasound bioeffects associated with therapeutic uses, although often dramatic and quite reproducible, may have little bearing on the diagnostic use of this energy form.

Diagnostic Exposure Levels

The ultrasound energy to which patients are exposed from modern diagnostic ultrasound systems depends on the particular application. Table 1 shows representative values of exposure measurements for medical diagnostic ultrasound units as compiled by O'Brien.[22] Exposure values vary widely and are highest for cardiac pulsed Doppler systems. It should be recognized that the maximum values for spatial peak temporal average intensity cited in Table 1 for some types of diagnostic systems exceed the "magic number" of 100 mW/cm², as cited in the American Institute of Ultrasound in Medicine (AIUM) "Statement on Mammalian In Vivo Ultrasonic Biological Effects" (see below). This information should not be interpreted as indicating that these higher intensities are associated with a definite risk of biologic adverse effects. The AIUM statement should be correctly interpreted as indicating that no bioeffects have been well documented and confirmed in mammalian tissues exposed to intensities below 100 mW/cm², not that exposures in excess of this intensity level have been associated with bioeffects. In addition, as was alluded to above, the AIUM statement is based in part on data obtained utilizing relatively broad-beam therapeutic ultrasound systems. Because modern ultrasound diagnostic imaging systems generate narrower, focused beams, it is probable that certain mechanisms of ultrasound bioeffects (such as thermal mechanisms) would be less significant with a narrow beam than with a broad beam. A recent bioeffects conference of the AIUM has addressed many of these issues, and the report from this committee should be forthcoming shortly.

In Vitro Data

Studies[28] on isolated cells have indicated that ultrasound exposure may lead to cell lysis and that less dramatic ultrastructural changes may lead to alterations in plasma membrane integrity. Furthermore, ultrasound of high intensity may produce degradation of deoxyribonucleic acid (DNA) in aqueous preparations; several other morphological and func-

tional alterations have been identified in vitro.[28] Two important factors must be remembered in reviewing these in vitro results. First, cavitation is probably the major mechanism in producing cell lysis and some of the DNA alterations.[36] Although cavitation can be reproduced in vitro, there is scant evidence that cavitation occurs in biologic tissues after exposure to diagnostic ultrasound. Second, other changes in cellular preparations, including excessive heating, free radical formation, and others,[36] are responsible for some of the effects, and these conditions are unlikely to occur in clinical ultrasound examinations of biologic tissue.

One of the recent areas of intense interest in bioeffects has been in the measurement of genetic effects based on sister chromatid exchanges used as a bioassay for putative mutagenic effects of ultrasound.[37,38] Although a few studies have suggested that the incidence of sister chromatid exchanges is increased after ultrasound exposure, the vast majority of studies in this area have been negative, showing no increase in sister chromatid exchanges in ultrasound-exposed cells.

In summary of the in vitro data, ultrasound at sufficiently high intensity and under appropriate conditions may cause a variety of sublethal and/or lethal bioeffects. These results should not cause undue concern to the clinician because the in vitro conditons permit mechanisms such as cavitation to be predominant, and these mechanisms are unlikely to occur in biologic tissue.

In Vivo Experimental Studies

The literature on in vivo experimental bioeffects has involved a broad variety of animal experiments. Those of most obvious interest are the studies that involve the search for possible genetic alterations caused by ultrasound exposure. This concern is understandable, since a large proportion of pregnancies currently include fetal exposure to ultrasound. Thus a substantial amount of research has gone into studies of ultrasound bioeffects in fetal mice and other species. High intensity ultrasound can potentially cause gross tissue damage either from heating or from cavitation mechanisms.[22,28] Gross morphological changes such as these have never been confirmed when utilizing the lower intensity ultrasound characteristic of imaging systems. More subtle functional alterations may occur with diagnostic ultrasound imaging levels. In particular, some investigators have identified the possibility of decreased birth weight in mice exposed to ultrasound during fetal life.[26] Many (if not most) of the fetal mouse birth weight studies have been conducted at therapeutic ultrasound intensities. There is continuing controversy over whether fetal weight reduction may occur when utilizing diagnostic ultrasound exposure levels. Although there is much negative literature in this area, further research is probably indicated to attempt to clarify the risk, if any, of fetal birth weight reductions caused by ultrasound in mammalian studies. As is reemphasized later, no convincing evidence of low birth weight from human fetal exposure has been documented and confirmed.

Human Epidemiologic Studies

At least three important pieces of information can be brought to bear on the issue of bioeffects on the basis of a review of the literature on human epidemiology. First, extraordinarily wide experience with clinical ultrasound in the heart and other organs has failed to reveal adverse biologic effects. Large international surveys of hundreds of thousands of patients have documented virtually no adverse effects from ultrasound.[2,39] These types of studies may be criticized on the basis of their survey nature. Thus subtle effects were not necessarily assessed, and the design of the studies was such that specific prospective hypotheses may not have been pursued. Furthermore, it is well known to clinicians and researchers alike that subtle increases in naturally occurring adverse outcomes in any type of study may not be recognized unless a large population is evaluated prospectively. Despite these considerations, the absence of proved deleterious effects of diagnostic ultrasound after over 20 years of use is most comforting.

In addition to large epidemiologic studies, a second area of interest includes the results of studies of specific outcomes, such as the occurrence of birth weight reductions in humans exposed to ultrasound in utero. This concern has been raised in part on the basis of the animal studies cited above. Conflicting results have been reported in the literature on human birth weight, but systematic reviews of these studies have yielded the conclusion that there is no association between ultrasonic exposure and birth weight.[27] This conclusion is based on the great predominance of negative results in studies to date conducted on this issue.

A final issue is whether ultrasound exposure in utero may cause other effects that are more subtle than a reduction in birth weight. Reviews of the

literature on ultrasound epidemiology suggest that major congenital anomalies are not produced by exposure to diagnostic ultrasound. Some questions remain concerning the possibility of subtle effects of ultrasound, and research into these areas is suggested by some authors.[27] Despite these generally negative results, continuing surveillance and further prospective evaluations of ultrasound safety are indicated because of the remaining possibilities of subtle increases in the incidence of naturally occurring anomalies associated with ultrasound exposure.

Studies on Nonreproductive Tissues In Vivo

Because the echocardiographer is mainly interested in the application of ultrasound energy to the thorax (with the exception of those performing fetal echocardiography), it would be of interest to evaluate epidemiologic literature oriented toward determining the presence or absence of adverse effects on cardiac and other thoracic tissue. We are unaware of prospective or retrospective studies in which any adverse effects of ultrasound to nonreproductive thoracic tissue have been documented.

Summary

The widespread use of ultrasound for over 20 years throughout many parts of the world has resulted in virtually no documentation of adverse biologic effects at the intensities of diagnostic ultrasound imaging systems. Statistical considerations suggest that subtle effects might be missed if not sought in carefully controlled prospective studies with large numbers of patients. Furthermore, in vitro and in vivo ultrasound bioeffects have been documented, albeit often under exposure conditions that were not representative of the clinical situation. Thus our overall view of the literature on bioeffects is that further research into obstetric uses of ultrasound is probably indicated, given the ubiquitous exposure of the population to ultrasound in utero. Echocardiographic applications of ultrasound appear so far to be without any identified risk.

AIUM/NEMA SAFETY STANDARD AND RELATED DOCUMENTS

The "Safety Standard for Diagnostic Ultrasound Equipment" was approved in 1981 after being developed over several years by a joint group of the Bioeffects and Standards Committees of the AIUM and the Ultrasound Imaging Section of the National Electrical Manufacturers Association (NEMA).[23] For the first time representatives from official organizations of manufacturers and "users" worked together and agreed on methods for defining and measuring ultrasound field strengths and codified acoustic labeling requirements. The document includes sections on electrical safety and ultrasound safety guidelines. There are six appendexes: (1) bioeffects and biophysics related to diagnostic ultrasound equipment; (2) survey of exposure levels from current diagnostic ultrasound systems; (3) rationale for acoustic labeling requirements, ultrasound safety guidelines, and definitions; (4) rationale for acoustic measurement methods; (5) hydrophone calibration procedures; and (6) rationale for electrical and mechanical safety requirements. This standard is currently under revision by a joint AIUM and NEMA task group.

The section on ultrasound safety has been updated by the AIUM Bioeffects Committee in 1982 and 1983 and expanded in the document "Safety Considerations for Diagnostic Ultrasound" issued in 1984.[5] The introduction notes that the question of the safety of ultrasound has no simple, absolute answer. In considering this question, the AIUM formulated three statements that offer guidance to the judicious application of ultrasound in medical practice, and these are reproduced from this document in full.*

> **Statement on Clinical Safety** (revised October 1983)
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> Diagnostic ultrasound has been in use for over 25 years. Given its known benefits and recognized efficacy for medical diagnosis, including use during human pregnancy, the AIUM herein addresses the clinical safety of such use: No confirmed biological effects on patients or instrument operators caused by exposure at intensities typical of present diagnostic ultrasound instruments have ever been reported. Although the possibility exists that such biological effects may be identified in the future, current data indicate that the benefits to patients of the prudent use of diagnostic ultrasound outweigh the risks, if any, that may be present.
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> **Statement on Mammalian In Vivo Ultrasonic Biological Effects** (October 1982)
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> In the low megahertz frequency range there have been (as of this date) no independently confirmed

*American Institute of Ultrasound in Medicine. Safety considerations for diagnostic ultrasound. Bethesda, Maryland: AIUM publication 316, 1984:3, 10, 12.

significant biological effects in mammalian tissues exposed to intensities below 100 mW/cm² (spatial peak, temporal average as measured in a free field in water). Furthermore, for ultrasonic exposure times less than 500 seconds and greater than one second, such effects have not been demonstrated even at higher intensities when the product of intensity and exposure time is less than 50 joules/cm² (exposure time refers to 'total time'; this includes off-time as well as on-time for a repeated pulse regime).

Statement on In Vitro Biological Effects (October 1982)

It is often difficult to evaluate reports of ultrasonically induced in vitro biological effects with respect to their clinical significance. The predominant physical and biological interactions and mechanisms involved in an in vitro effect may not pertain to the in vivo situation. Nevertheless, an in vitro effect must be regarded as a real biological effect.

Results from in vitro experiments suggest new end-points and serve as a basis for design of in vivo experiments. In vitro studies provide the capability to control experimental variables and thus offer a means to explore and evaluate specific mechanisms. Although they may have limited applicability to in vivo biological effects, such studies can disclose fundamental intercellular or intracellular interactions.

While it is valid for authors to place their results in context and to suggest further relevant investigations, reports which do more than that should be viewed with caution.

Another related AIUM document is "Evaluation of Research Reports: Bioeffects Literature Reviews," published in 1984.[40] This addresses an important problem touched on in the AIUM statements above: the literature on bioeffects is potentially confusing in that there are many claimed effects that do not document exposure conditions and others that have not been reproduced despite attempts (sometimes repeated attempts) to do so. This 1984 document is an attempt by the AIUM Bioeffects Committee to give some perspective and critical reviews to the literature. The need to do so shows a perceived weakness in the literature and cautions investigators who are unfamiliar with the literature on bioeffects to adopt a critical approach.

OVERVIEW OF REGULATORY PROCESSES

Much recent attention has been focused on the process of regulating medical diagnostic and therapeutic devices in general[41] and ultrasound imaging systems in particular. One example of the latter is the recent concern expressed by clinical ultrasound imaging experts over the proposed Food and Drug Administration rule that would require a label on some portion of the imaging system, implying potential fetal harm from clinical ultrasound imaging and/or Doppler devices.[42] A brief review of the federal regulatory process may help to interpret these and other recent and continuing events.

Since 1976, the FDA has been responsible for and has had a congressional mandate to regulate medical devices, on the basis of the Medical Device Amendments to the *Federal Food, Drug, and Cosmetic Act*.[41] The regulatory process set up by the amendments is complex, in part because of the extremely broad definition of device, resulting in literally tens of thousands of individual products that fall under these regulations. The regulatory process obviously has a major impact on the nature of ultrasound imaging systems coming to market, on the circumstances under which clinicians may use them, and ultimately on reimbursements by the Health Care Financing Administration for clinical examinations.

The regulatory process for ultrasound imaging systems in essence began with the 1976 amendments. Many excellent ultrasound imaging systems were in wide use before that time and were generally considered safe and effective. It is therefore not surprising that at present a major regulatory decision relating to approval of a particular device for marketing is whether the new system differs substantially from systems in use before 1976. In fact, the two methods to marketing approval open to a manufacturer of a new ultrasound imaging system are (1) to establish that a new system is "substantially equivalent" in safety and effectiveness to similar systems marketed before 1976; and (2) to establish safety and effectiveness anew, given that a device is not equivalent to "preamendment" devices.[41] This latter process (new demonstration of safety and effectiveness) is termed *premarket approval* and requires a premarket approval application, an extensive procedure. A new intended use of a device that is otherwise similar to a preamendment device may require a complete premarket approval application, since effectiveness for the new intended use would need to be established.

The establishment of substantial equivalence of a new device compared with systems used before the amendments requires that the manufacturer of the new device notify the FDA of its intent to market the system, a process termed *premarket notification*. The premarket notification process is relatively less rigorous and is to be differentiated from premarket

approval, the more rigorous process requiring a premarket approval application. The requirement for premarket notification before marketing a putatively substantially equivalent device is found in section 510(k) of the amendments; thus the term *510(k)* has come to be used interchangeably with *premarket notification* of intention to market a device that is purportedly equivalent to a system used before 1976.

One of the important criteria used to establish whether a new ultrasound imaging system is comparable to preamendment systems is an examination of the relative acoustic outputs of the new and preexisting systems. Under the assumption that particular threshold levels of acoustic output can be identified to be indicative of unacceptable risk, one would assume that an absolute output would be utilized as a measure of new product safety. However, as indicated earlier, although ultrasound is capable of causing biologic damage at high intensities, the power outputs characteristic of most (if not all) clinical imaging systems are free from evidence of human tissue damage. Thus an arbitrary standard for product marketing approval has been indentified as the acoustic outputs of preamendment imaging systems. Therefore the de facto acceptable acoustic output of a new ultrasound imaging system is the level of output characteristic of imaging systems before 1976, as identifiable by the Center for Devices and Radiological Health (CDRH) of the FDA. The CDRH has published a "510(k) Guide for Measuring and Reporting Acoustic Output of Diagnostic Ultrasound Medical Devices."[43] This document contains much specific information on definitions, test methodology, acceptable preamendment device intensities, and other details needed to establish that a new device is, in the acoustic output sense, substantially equivalent to devices before 1976.

As one might expect, the decade of progress in ultrasound imaging since the 1976 Medical Device Amendments has brought with it changes in virtually every aspect of imaging system design and operation. In particular, the widespread acceptance of the importance of Doppler examinations in echocardiography has altered and actually increased the acoustic outputs of clinical imaging systems. Although still not associated with proved human biohazards, some of the outputs of newer devices appear to exceed those of some preamendment systems. Thus the CDRH has updated the 510(k) guide to (1) indicate new limits of outputs, which may be used to satisfy the substantial equivalence criterion (the CDRH recently discovered some devices used before 1976 that had higher outputs than the originally designated preamendment limits); (2) indicate that devices with outputs higher than even the new higher limits might still be considered for 510(k) approval on the basis of ". . . such factors as product labeling, design and performance, including improved clinical effectiveness . . ."[44,45]; and (3) indicate the requirement for labeling of the system as to safety criteria. This latter topic, system labeling, brought with it tremendous controversy. The clinical imaging community, through such organizations as the American Society of Echocardiography and AIUM, and the manufacturing community, through NEMA, protested the unprecedented requirement of labeling that would indicate a putative risk associated with an ultrasound examination (such as the label that read *not for fetal use*). The labeling requirements were actually rescinded, and new suggestions were raised. At the time of this writing, the issue of new product label requirements as part of the 510(k) process has not been resolved. Nonetheless, this issue is an example of the interaction between the CDRH (in essence, the FDA), the clinical and/or professional communities, and product manufacturers in the approval of new ultrasound imaging systems. However one interprets the current state of the literature on ultrasound bioeffects, ideally future regulatory decisions affecting the use of ultrasound imaging systems will be made in an environment of free dialogue among the FDA, clinicians, physicists, engineers, statisticians, epidemiologists, and professional and/or manufacturing organizations. The formal establishment of such a dialogue can only help to expedite and strengthen the regulatory process and to put subsequent decisions on a firmer footing.

CONCLUSION

Echocardiography is an extremely widely used noninvasive imaging technique that is capable of delineating an extraordinary amount of information on heart size, shape, and function in health and disease. The major attributes of ultrasound that will guarantee its continued clinical popularity include its relatively low cost, noninvasive nature, diagnostic accuracy, painlessness, and perhaps among the most important factors, the virtual lack of evidence of clinically important bioeffects. Despite the lack of well-documented biohazards in humans, ultrasound has the clear capacity for biologic damage at sufficiently high intensities. This knowledge of potential bioef-

fects should keep the community of clinical echocardiographers alert to new scientific findings that pertain to bioeffects and to new information concerning the acoustic outputs relevant to such effects. Similarly, the awareness of ultrasound's potential for bioeffects should make echocardiographers more informed consumers of imaging systems, better able to communicate concerning acoustic outputs and their relevance. The outstanding safety history of ultrasound, the complete lack of documented bioeffects in nonreproductive tissues (when used at the intensities of clinical diagnostic systems), and the low risk predicted by studies of ultrasound bioeffects mechanisms should combine to support the high level of confidence in the safety of this excellent method of cardiac imaging.

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