

Ultrasound Bioeffect Issues Related to Obstetric Sonography and Related Issues of the Output Display Standard

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Ultrasound has had a profound influence on the practice of medicine, especially in obstetrics. It has been four decades since the first ultrasonic devices were developed to provide an image of the fetus. The early studies with these devices showed a potential to provide high-resolution information about the fetus, information that, if obtained by other techniques, could pose significant risks. Ultrasound did not appear to be associated with any known hazards. Diagnostic ultrasound also gained acceptance because it is convenient to use, comfortable for the patient, and not very expensive.

There continues to be a general belief in the medical community that ultrasound does not represent a risk to mother or fetus, but academic and government research scientists have continued to investigate and evaluate the risks. Some of these investigators have argued that the appropriate research has not been done to support a reliable assessment of the risks associated with human exposure to ultrasound. It could be argued, however, that there is always an insufficient data base to "prove" a modality totally safe.

The fact that there continues to be concern for the safety of ultrasound represents a continued interest by the clinical and basic science community in seeing that the use of this modality remains safe. Continued research will improve our data base and increase our confidence, and, if a serious biologic effect is identified, which has not yet been the case, such information will then be disseminated to the clinical community so that appropriate risk-benefit decisions can be made.

It has been over two decades since the first major efforts to assess the risk of ultrasonic energy were made.^{1,2} Since then there have been numerous reviews and assessments.³⁻³⁰ The use of diagnostic ultrasound in obstetrics continues to increase worldwide despite efforts by several national^{10,13,15,24,27,29} and international organizations^{11,25,28} and the RADIUS Study³¹ to restrict its use to clinically indicated examinations. The basic status regarding risk assessment has remained essentially unchanged during this time, that is, the studies necessary to support a reliable

assessment of the risks associated with human exposure to ultrasound have not been undertaken; however, this has not adversely impacted diagnostic ultrasound's necessary and valuable applications in clinical medicine. This chapter reviews the understanding of ultrasound-induced biologic effects relative to the applications in fetal medicine and further addresses issues of the newly approved Output Display Standard.³²

ULTRASONIC BIOPHYSICS

Ultrasonic biophysics³³ is the study of mechanisms responsible for how ultrasound and biologic materials interact. As shown in Fig. 2-1, when one studies how ultrasound affects biologic materials, it can be viewed as a bioeffect study or a risk study. On the other hand, the study of how tissue affects the ultrasound wave can be viewed as the basis for diagnostic ultrasound. Thus, an understanding of the interaction of ultrasound with tissue provides the scientific basis for understanding image production and risk assessment.

The emphasis of ultrasonic biophysics studies in this chapter is on how mechanisms responsible for how ultrasound and biologic materials interact. Research in this area has shown that ultrasound can produce changes in living systems. This knowledge comes from the fundamental laboratory studies that form the basis for an understanding of the known mechanisms by which ultrasound can affect living systems.^{17,20,26,30,33,34} These mechanisms can be classified in terms of whether a temperature increase (thermal) or a mechanical effect (usually bubble-like or cavitation-like activity) is believed to be the principal cause for the given biologic effect.

When discussing bioeffects studies and biophysical mechanisms, whether thermal or cavitational, there are selected exposure quantities that need to be completely characterized. The source ultrasonic power can be completely characterized in vitro in a lossless medium (ie, water) as is

required of equipment manufacturers by the Food and Drug Administration (FDA).³⁵⁻³⁷ In fact, depending on the intended clinical use, ultrasound equipment can be designed to specific acoustic output characteristics and tested to ensure performance within defined output limits. The relevance of this process and in vitro acoustic pressure data, obtained in a lossless medium, to in situ exposure levels remains uncertain. From a regulatory standpoint, the FDA uses a homogeneous tissue model where it is assumed that the ultrasonic attenuation coefficient of tissue between the ultrasound transducer and the conceptus, for example, is 0.3 dB/cm-MHz.³⁵⁻³⁷ Although this ultrasonic attenuation coefficient value is believed to be conservative, thereby modeling the "maximum exposure or worst-case" risk, in vivo studies have shown that the in vivo minimum insertion loss value for human pregnancy at 20 weeks' or less gestation is 0.14 dB/cm-MHz.³⁸ Thus, in certain cases, the FDA derating value could significantly underestimate acoustic exposures to sensitive embryonic or fetal tissues. This risk is further compounded by the FDA change in the maximum allowable derated (based on a derating factor of 0.3 dB/cm-MHz) $I_{SPTA,3}$ (derated spatial peak, temporal average intensity) from 94 to 720 mW/cm² for obstetric ultrasound equipment manufacturers.³⁶ The ".3" in the subscript denotes the specific derating factor of 0.3 dB/cm-MHz.

When the FDA initiated the regulation of diagnostic ultrasound equipment in the mid-1980s,³⁵ it set application-specific intensity limits that manufacturers could not exceed (see Table 2-1). Note that for the "fetal imaging and other" application, the derated $I_{SPTA,3}$ could not exceed 94 mW/cm². Likewise, the derated spatial peak, pulse average intensity ($I_{SPPA,3}$), and derated maximum intensity ($I_{m,3}$) could not exceed their listed values. These limits were (and are) *not* based on safety considerations but rather on the

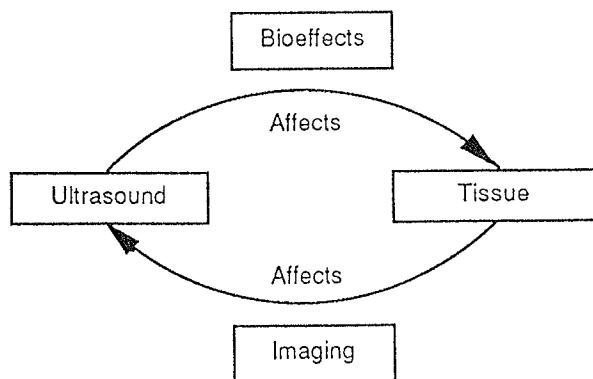


Figure 2-1. View of ultrasonic bioeffects studies.

TABLE 2-1. FDA'S PREAMENDMENTS LEVELS OF DIAGNOSTIC ULTRASOUND DEVICES^a

	Derated Intensity Values		
	$I_{SPTA,3}$ (mW/cm ²)	$I_{SPPA,3}$ (W/cm ²)	$I_{m,3}$ (W/cm ²)
Cardiac	430	190	310
Peripheral vessel	720	190	310
Ophthalmic	17	28	50
Fetal imaging and other ^b	94	190	310

^aHigher non-application-specific levels are now allowed if the diagnostic ultrasound system is approved through the Output Display Standard procedures.³⁵

^bAbdominal, intraoperative, small organ (breast, thyroid, testes), neonatal cephalic, adult cephalic.

known maximum output limits of diagnostic ultrasound equipment at the time when the Medical Devices Amendments were enacted in May 1976, hence the term *pre-amendments levels*. All of these dosimetry quantities are defined in selected references.^{12,21,39}

When considering dosimetry quantities related to the interaction of ultrasound with tissues, the intensity of the beam is important because it has been most commonly reported and because the FDA³⁵ (see Table 2-1) regulates diagnostic ultrasound equipment based on intensity. It should be noted, however, that intensity is not a dosimetric quantity and is thus flawed as a predictor of heating and cavitation in tissue. Yet, most of the contemporary and earlier bioeffect literature reports their results in terms of intensity quantities, as will be seen in this chapter.

Diagnostic ultrasound manufacturers can still have their equipment approved through the application-specific limits listed in Table 2-1; however, manufacturers can also have their equipment approved under the provisions of the Output Display Standard,^{32,36,37} in which case the non-application-specific regulatory upper limits are based on the $I_{SPTA,3}$ of 720 mW/cm², and the mechanical index (MI) of 1.9 (the MI replaces both $I_{SPPA,3}$ and $I_{m,3}$). In doing so, provisions must be made available for the thermal index (TI) and MI to be displayed. The following discussion describes the biophysical basis of these indices, the definition of these indices, and the conditions under which they are displayed.

Thermal Mechanism

When high-frequency ultrasound is propagated into an attenuating material such as soft tissues, the amplitude of the ultrasonic wave decreases as it traverses deeper structures. This attenuation results in an overall loss in the wave amplitude that is due to either absorption or scattering. *Absorption* is a mechanism that represents that portion of the wave's energy that is lost by its conversion into heat; *scattering* can be thought of as that portion that changes direction, some of which is reflected as echoes that produce the images seen on the screen of the scanner.

Hyperthermia is a proven teratogen in experimental animals^{40,41} and, although controversial,⁴² is considered by some investigators to be a human teratogen under certain circumstances.⁴³ Since biologic tissues exposed to ultrasound are capable of absorbing energy with the resultant production of heat, a temperature rise may occur when the rate at which heat is produced is greater than the rate at which heat is removed.^{6,34} The increase in temperature produced by ultrasound can be calculated using mathematical modeling techniques⁴⁴⁻⁴⁹ and has been estimated for a variety of exposure conditions in vivo.^{13,23,27,49-54} It has been shown that temperature elevations ≥ 2.5 to 5.0°C can occur with ultrasound after ≥ 1 -hour exposures.^{24,29,55,56}

A substantial increase in intrauterine temperature has not been considered possible in a human clinical setting as the output levels of commercial systems and the methods of

exposure have been considered to be significantly different from those employed in experimental studies. Based on mathematical modeling techniques it has been shown that the low intensities and short insonation times should result in negligible temperature elevations (ie, <1.0°C). In addition, the dissipation of heat by conduction and circulating blood (perfusion) could further decrease the rise in intrauterine temperature. An evaluation of the world's literature on the biologic consequences of hyperthermia concluded that there is an absence of any thermally mediated effects on animals below 39°C.⁵⁶ The actual elevations that occur within embryonic or fetal tissues from diagnostic ultrasound equipment exposures have not been sufficiently evaluated in utero, however. The potential effects of any change in the basal temperature of specific areas of the conceptus (particularly if repetitive) are also not known.

Cavitation Mechanism

Cavitation can be discussed under two general categories, namely "transient" and "stable" cavitation,⁵⁷ both of which involve the occurrence of gaseous bubble formation. Transient cavitation refers to a relatively violent activity (ie, bubble collapse) in which "hot spots" of high temperature, high pressure, or both occur in very short (microsecond) bursts. These bursts may be accompanied by localized shock waves, by the generation of highly reactive chemical species such as hydroxyl radicals, or by both. In contrast, a much less violent form is stable cavitation, which is associated with the vibration of these gaseous bubbles. The nature of this form of cavitation consists of a micron-sized gaseous body, which, because of the presence of an ultrasound field, may oscillate or pulsate. When such oscillations are established, the liquid-like medium immediately adjacent to the gas bubble flows or streams (termed microstreaming),⁵⁸ which has been shown to produce stresses sufficient to disrupt cell membranes.

Although a known phenomenon in regard to ultrasound, cavitation has been difficult to document in mammalian systems. The presence of small gaseous nuclei (bubbles) is clearly plausible, as evidenced by the problems divers may encounter with decompression sickness. Many studies have been performed with *Drosophila melanogaster* due to the natural presence of air in these organisms.⁵⁹ Although little work has been done regarding cavitation and the mammalian fetus, it has been shown in vivo that ultrasonically induced bubble activity can result in lung damage in adult mice.⁶⁰⁻⁶⁴ These observations correlate well with frequency-dependent in vitro cavitation experiments.⁶⁵ In an effort to confirm whether or not the lung sensitivity observed in adult mice was related to the presence of air, in utero mouse fetuses were exposed to high peak ultrasonic pressures (20 MPa) on the 18th day of gestation.⁶¹ Results indicated no significant effects on fetal tissues exposed in situ, including the lung; peak acoustic pressure levels were roughly ten times the output required for damage in adults in

prior studies.⁶⁰ As anticipated, marked intestinal and lung hemorrhages were noted in the dams of these fetuses at the higher exposures. These studies support the hypothesis that cavitation- or bubble-like activity may *not* be a significant concern in relation to the fetal lung, although the potential for cavitation nuclei in other regions of the fetus is unknown.

DOSE-EFFECT APPROACH

Experimental studies consist of exposing the specimen to ultrasound and evaluating whether or not there have been any biologic changes that can be attributed directly to the exposure. The choice of exposure quantity and the type of biologic effect are critical elements of the experimental protocol. Exposure quantity variables include, but are not limited to, the following: pulsed or continuous wave conditions; frequency; power; spatial average, temporal average intensity (I_{SATA}); I_{SPTA} ; spatial peak, pulse average intensity, if pulsed (I_{SPPA}); peak rarefactional pressure (p_r); unfocused or focused fields; and exposure duration. If a diagnostic system is the exposure source for the experiment, then its output quantities generally are not easy to control and are quite challenging to measure. Only exposure duration can be easily varied with a diagnostic system because most of the other output quantities are fixed within the system. On the other hand, when specially designed exposure systems are used, virtually every exposure quantity is under the investigator's control. It is essential to have control over all exposure quantities because only then can dose-effect studies be properly planned and conducted.

What is meant by *dose*? It is quite difficult to determine the exposure time that the human fetal heart, for example, is undergoing during an examination, especially when the ultrasonic beam is rapidly scanning from the transducer as-

sembly and the transducer assembly is also being moved. Under such conditions the ultrasonic dose is quite difficult to quantify. Further, it is not known which of the various ultrasonic intensity quantities are relevant in terms of the dose determination. Consider the fact that the very high I_{SPPA} acts for only a millionth of a second, and this action repeats itself every thousandth of a second, whereas the very much lower I_{SATA} acts for quite a long period of time. Dose for the former could be much lower than that for the latter.

Dose-effect studies are necessary for two important reasons: (1) they provide the capability to extrapolate the amount or kind of effect at the doses used experimentally to the dose generated by diagnostic systems (it is easier to determine what is generated than what a tissue receives), and (2) they provide the fundamental basis from which the biophysics mechanisms causing the effect can be evaluated (ie, was it due to heating, cavitation, or some other cause?). To obtain measurable and highly repeatable biologic effects in experimental studies, the dose conditions are generally higher than those used diagnostically. The dose is varied over this higher range of values, and the effect is evaluated. In this way, extrapolation to the lower diagnostic dose levels is placed on a scientific basis. Let us consider two examples. In one case, the effect might be proportional in such a way that, when extrapolated, it does not go to zero (or to a normal level) until the dose goes to zero. This would be considered a *no threshold effect*. In another case, the experimental study could yield an effect that goes to zero (or a normal level) at some nonzero dose. This would be an example of a *threshold effect*. In the first case, the degree of the effect would have to be evaluated when extrapolated to diagnostic levels. In the latter, the evaluation would depend on where the threshold occurred.

Consider the mouse dose-effect fetal weight data shown in Figure 2-2. The laboratory observations that ultrasonic exposure in utero can cause weight reduction in mouse

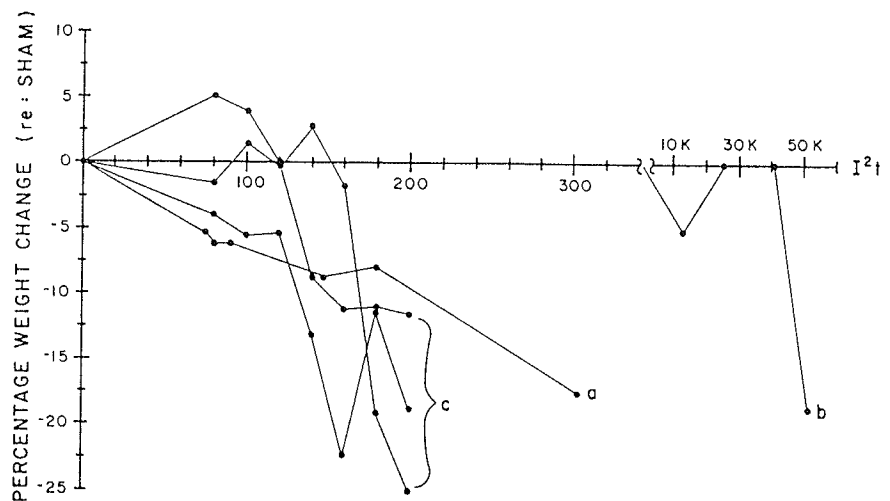


Figure 2-2. Summary of three mouse fetal weight studies in terms of the dose quantity I^2t . Curves a, b, and c represent data from references 66, 67, and 68, respectively.

fetuses have been shown by three research groups using three different strains of mice.⁶⁶⁻⁶⁸ Figure 2-2 graphically summarizes in a unified way the three published studies⁶⁶⁻⁶⁸ that reported statistically significant effects of fetal weight reduction from in utero exposure to ultrasound wherein the results are represented by the percentage weight change (against sham) as a function of the calculated dose parameter I^2t . All three studies graphically show that as the value of I^2t increases, the fetal weight (against sham) generally decreases. These fetal weight studies are summarized in greater detail.²⁶

If we were to apply dose-effect curve **a**⁶⁶ (see Fig. 2-2) to a clinical exposure condition for purposes of assessing risk, then we would first examine the upper value of the dose parameter I^2t for pulse-echo scanners operating in B-mode only.¹² For a single pulse, I_{SPPA} might be 500 W/cm² and the exposure time (here the pulse duration) about 1 μ s, yielding an I^2t value of 0.25. For the time average case, I_{SPTA} could be 200 mW/cm², and the exposure time (here the length of the exam for maximum effect) is about 30 minutes, yielding an I^2t around 72. Of course, this latter case would require examining the same tissue volume for the entire length of time. This might not be the situation with pulse-echo scanner operating in B-mode only but is quite possible for spectral Doppler. The point made is that one is in a better position scientifically to examine what the effect might be under clinical conditions with a dose-effect model. The model would have to be validated for such applicability, of course.

RISK ASSESSMENT APPROACH

Given the current understanding of ultrasonically induced biologic effects, it is difficult to argue against statements such as "diagnostic ultrasound is not harmful to the fetus." Experimental studies cannot be used to prove diagnostic ultrasound safe. Rather, what such studies will provide, if properly planned and executed, are data to aid in the overall assessment of risk associated with exposure to ultrasound. The term *safe* can imply the *complete* absence of an effect—that the procedure involves no risk. It simply is not possible, however, to prove that ultrasound, or for that matter any agent, produces no effect whatsoever at the levels employed diagnostically. The actual use of the word *safe* in medicine is also vague as it almost never refers to the absence of an effect, and the term can also imply the *apparent* absence of an effect. A more useful and workable approach, therefore, is to examine the *risk* associated with ultrasonic exposure.

Some 35 years after the Curies discovered piezoelectricity in 1880,⁶⁹ the first use of ultrasonic energy was developed—underwater acoustic echoes were bounced off submerged objects.^{70,71} During the course of this work, the first reported observation was made that ultrasonic energy had a

lethal effect on small aquatic animals.⁷² The first extensive investigation of the phenomenon confirmed that ultrasonic energy could kill small fishes and frogs within 1 to 2 minutes.⁷³ In perhaps the first review paper of ultrasonically induced biologic effects,⁷⁴ the physical, chemical, and biologic effects of ultrasound were evaluated. The effects on cells, isolated cells, bacteria, and tissues were summarized, with a view toward identifying the responsible mechanism. The ultrasonic exposure conditions in this early work were not well characterized, but the intensity levels were undoubtedly very much higher than those currently in clinical use.

In the early pioneering studies in which the ultrasonic exposure conditions were more carefully controlled and specified, sciatic nerve paralysis was easily produced in the frog^{75,76} and lesions were produced in central nervous system tissue.⁷⁷ In addition, high-intensity ultrasound was employed to produce lesions in adult cat and rat brain,⁷⁷⁻⁸³ adult rat and neonatal mouse spinal cord,^{77,83,84} adult frog muscle,^{85,86} rabbit blood vessel,⁸⁷ rabbit kidney and testicle,⁸⁸ and rabbit ocular tissue.⁸⁹⁻⁹¹ The ultrasonic intensities were much higher than those used in diagnostic ultrasound and, for the most part, these studies caused well-characterized and rather severe tissue damage. They have been extremely important in the elucidation of fundamental interaction processes. In terms of risk assessment, these studies have supported the view that diagnostic ultrasonic exposure conditions would more than likely not produce acute, gross irreversible damage.

These high-intensity studies further aided in recognizing the important fact that, at sufficient output levels, ultrasound is capable of destroying biologic material. An approach, therefore, to the question of assessing the risk from ultrasound is (1) what biologic systems are most sensitive to ultrasound? and (2) what exposure levels impose a significant risk on these systems?

This approach unfortunately has its difficulties. How does one determine significant risk? *Significant risk* usually means risk that is greater than some upper limit of acceptability. A benefit-versus-risk analysis is simple in principle but is not so easily implemented. An important consideration with respect to the evaluation of risk is an estimate of the extent of ultrasonic exposure that the patient receives. This may not give a good indication, however, as to the amount of ultrasonic energy that the patient population or a particular organ system receives because (1) the number of examinations a patient receives is generally unknown, (2) multiple examinations may be performed with different types of equipment, and (3) the amount of ultrasonic energy that a patient receives varies from exam type to exam type and from examiner to examiner. Whereas no statistically based survey is known to have documented the extent to which ultrasound is being used, a number of early indicators suggest that its use is increasing and that a large fraction of the human population will eventually be exposed, especially in utero.

In 1971, the FDA's Bureau of Radiological Health surveyed 301 out of 6306 short-term hospitals in the United States and found that 12% of the hospitals used diagnostic ultrasound.⁹² The same federal agency reported in its 1974 hospital survey that 35% of the surveyed hospitals used diagnostic ultrasound.^{93,94} This represented an almost 200% increase in use between 1971 and 1974 (assuming that the surveys were identical), for an annualized increase of 43% during this time period. The 1974 survey^{93,94} further showed that an estimated 16% of the obstetric services in the United States used diagnostic ultrasound and that about one third of all US births in 1974 were delivered in these hospitals. Additionally, it was estimated that 470,000 pregnant women were exposed in the United States to diagnostic ultrasound in that year with about 35 to 40% of these women being examined more than once. This is consistent with the 1984 report of the National Council on Radiation Protection and Measurement¹³ in which it was estimated that 40 to 60% of all ultrasonic imaging examinations were performed for obstetric purposes.

An examination of records in one US hospital setting⁹⁵ for two different years, 1975 and 1978, indicated that in 1975, 11% of the lowest risk pregnancy population was examined with ultrasound whereas 21% of that same risk population was examined in 1978. For the highest risk pregnancy population, these percentages were 66 and 76% for 1975 and 1978, respectively. An evaluation of these data showed that the use of ultrasound in the lowest risk pregnancy population was increasing at an annualized rate of about 25%; for the highest risk population it was about 5%. The rate of increase was greater in the lowest risk population, which probably did not generally present with clinical problems. In the population that exhibited clinical problems, the use was much greater, but the increase in use was not very high, owing perhaps to the fact that ultrasound was a relatively well-established diagnostic tool for this population of patients.

Sales growth information indicated that, in 1976 the ultrasonic industry's annual US dollar sales were around \$30 million⁹⁶ and for the following year about \$40 million.⁹⁷ In the next 4 years, estimates of annual sales were \$50, \$79, \$170, and \$214 million.¹⁰ An increase from \$30 million to \$214 million from 1975 to 1980 represents an estimated average annual increase in sales of approximately 48%. While there are no known published reports of current sales information, comments from selected manufacturers suggest that sales figures are in the range of \$900 million in the US. In terms of the number of diagnostic devices, it was estimated that 3500 systems had been sold in 1976 and approximately 12,400 in 1982,⁹⁸ for an annualized increase of about 24%.

In countries other than the United States, no surveys or comparable data are available. In the United Kingdom, it was estimated that in the early 1970s the number of ultrasonic diagnostic examinations doubled every 3 years,⁹⁹ representing an annualized 26% increase. An international mail

survey, which included the United States, suggested that, between 1963 and 1971, there was an average annual increase in the use of clinical ultrasound of approximately 10%.¹⁰⁰ In West Germany, official guidelines adopted in 1980 recommended the use of two ultrasound examinations during pregnancy,¹⁰¹ and the Royal College of Obstetrics and Gynecology in the United Kingdom recommended that one screening ultrasonic examination be performed in every pregnancy. A survey in Canada suggested that between 340,000 and 620,000 patients were examined with diagnostic ultrasound in 1977.¹⁰² While there are no known published reports of current sales information worldwide, comments from selected manufacturers suggest that sales figures are in the range of \$2 billion.

SOME GENERAL OBSERVATIONS

Experimental studies of ultrasonic biologic effects can be classified into morphologic or functional alterations.¹⁰³ Morphologic or tissue damage is usually permanent or irreversible. Such studies have been essential to the understanding of the mechanisms responsible for ultrasonically induced alterations to biologic material. Ultrasound at high levels can cause damage to tissue by heating or by a phenomenon called *cavitation*, a general term used to describe the growth and subsequent dynamic behavior of gaseous bubbles produced in tissue by ultrasound. The action by ultrasound on these bubbles causes them to respond by producing large shearing forces within the bubble vicinity. These forces, in turn, can disrupt and destroy biologic tissues. Morphologic changes caused by both heating and cavitation have been identified and studied with very high ultrasonic intensities.

Biologic changes, such as biochemical values, pH, function, activity, weight, and so forth, are termed functional alterations. These changes are not necessarily permanent. An example of a functional alteration is fetal weight change.^{66,104} In general, much greater ultrasonic intensity levels are required to produce morphologic alterations as compared to functional alterations. The I_{SPTA} and I_{SATA} intensity levels used in the fetal weight studies were much less than those used for studying morphologic alterations. Had these higher intensity levels been used to expose the mouse fetuses in utero, irreversible damage to the fetuses, and perhaps death, would have been the result.

Scientists and clinicians tend to question research findings of others whether they agree or disagree with them. *Such questioning is essential in science.* It is interesting to observe, however, that the content of scientific conflict changes as the intensity level of ultrasound diminishes, especially with respect to ultrasonic bioeffect studies. Morphologic alterations are produced by quite high levels of ultrasonic energy. There is no conflict over whether or not the morphologic effect has occurred, but rather the scientific de-

bate centers on what caused the alteration (that is, heating, cavitation, or some other mechanism). These are the levels employed in the surgical application of ultrasound for which consistently well-defined, permanent biologic alterations can be produced. For example, three laboratories have independently confirmed that a highly focused ultrasonic beam can produce a lesion in mammalian (cat and rat) brain tissue.⁷⁹⁻⁸² Further, there is agreement that the effect has a threshold, and these investigators all agree as to the threshold. There is disagreement, however, as to what degree the effect is caused by a thermal mechanism or by cavitation.

At lower ultrasonic levels, usually within the therapeutic range, there are conflicting viewpoints as to whether or not and to what degree morphologic alterations have occurred. Most of the mouse fetal weight studies have been conducted at intensities in the therapeutic range (I_{SATA} : 0.5 to 6 W/cm²). There have been almost three dozen studies that have examined the effect of in utero ultrasonic exposure on fetal weight in either rats or mice.^{17,20,26} Within these studies there are a number of perplexing and conflicting observations. For example, under the identical exposure and experimental conditions, in one strain of mouse statistically significant fetal weight reduction was determined, whereas in another strain of mouse, there was no observed change in the fetal weight. Both of these observations have been further confirmed in independent laboratories. Thus, under biologic conditions that are not understood, consistent and confirmed observations have been obtained for both positive effects and negative effects.

For a third general category, at ultrasonic levels lower than those in the therapeutic range and sometimes into the diagnostic range (I_{SATA} : 0.1 to 100 mW/cm²), there are conflicting data as to whether or not a functional alteration occurred. This is aptly demonstrated in the numerous experimental studies that examined the effect of ultrasound on sister chromatid exchange (SCE) frequency (an indication of chromosome damage of which the biologic significance is unclear). Some of these studies have shown an effect when a diagnostic ultrasound device was used; however, others have reported no change in SCE frequency¹⁴ at diagnostic levels and at levels much higher than therapy. A study by Liebeskind and associates¹⁰⁵ appears to have received the greatest attention because it indicated an increase in human lymphocyte SCEs (a positive effect) from a diagnostic system. In another study by the same authors,¹⁰⁶ however, also with a diagnostic system, no change in SCEs was reported (a negative effect). In the latter study, two different types of cells were used. There have been two other positive observations^{107,108} of increased SCEs, both with diagnostic levels of ultrasound. There have been at least ten other studies, however, some at diagnostic levels (both pulsed and continuous wave exposure conditions) and some at levels within or higher than therapeutic levels, that have reported no increase in SCEs. These 14 studies have been carefully and thoroughly reviewed by the American Institute of Ultra-

sound in Medicine's Bioeffects Committee.¹⁴ The committee's conclusion was that these studies do not suggest a hazard from exposure to diagnostic ultrasound.

One of the more controversial studies in the early 1970s of prenatal ultrasonic exposure of pregnant mice was conducted with a commercial fetal Doppler device.^{109,110} Fetal abnormalities were observed in both the exposed and control groups, the differences were not significant. The rate of fetal death, however, was increased significantly in the exposed group. The same researchers¹¹⁰⁻¹¹² found a statistically significant increase in fetal abnormalities in a different mouse strain. In both of these studies, pregnant mice were given an initial dose of sodium Nembutal that was effective for about 1 hour, after which the animals awoke and struggled in their harness for 4 hours; the ultrasound exposure duration was 5 hours. Edmonds¹¹³ drew attention to errors in the statistical analyses, the conclusions drawn, and the effective ultrasound power (about 280 mW). He concluded that the reported effects were related to a combination of prolonged binding of the mice and ultrasonic hyperthermia.

A significant reduction in the frequency of mitotic cells in surgically stimulated rat liver from diagnostic level, continuous wave ultrasound (I_{SATA} of 60 mW/cm²) was reported.¹¹⁴ This observation, however, was not able to be confirmed under virtually the identical research protocol, even when I_{SATA} ranged from 60 mW/cm² up to 16 W/cm².¹¹⁵

These are a few of the many studies reporting ultrasonically induced biologic effects at I_{SATA} levels below 100 mW/cm² for which attempts at replication failed. There are also many more studies for which no attempt has been made to replicate the original finding because, in general, research funding does not support this type of activity.

IN VIVO EXPOSIMETRY

The Output Display Standard³² that was approved in 1992 addresses one aspect of ultrasound dosimetry in which the user of diagnostic ultrasound equipment is provided with quantitative indices that relate to temperature increase, the TI, and the potential for cavitation, the MI, from the diagnostic ultrasound field. In its development, certain aspects of the tissue in which the ultrasound wave propagated had to be assumed in order to estimate in situ ultrasound exposure levels. Ultrasound exposimetry, a necessary component of ultrasound dosimetry, is thus concerned with the quantitative determination of ultrasonic exposure levels in biologic materials, and the development of quantitative tissue models is a necessary part of such studies.

There is, therefore, a need for realistic tissue models to predict in situ acoustic exposure levels from measurements of acoustic output made in water in order to have an improved basis for estimating risk. Both national^{13,24,27,29,32} and international^{25,28} organizations, as well as research

groups,^{38,116-123} have been evaluating models and guidelines, developing them, or both. For example, the FDA^{35,36} uses a homogeneous tissue model, also referred to as a de-rating model, in their 510(k) process, which is required by manufacturers and importers of diagnostic ultrasound devices in the United States to estimate in situ exposure levels.

In the past, reports by the FDA,¹⁰ National Council on Radiation Protection and Measurement (NCRPM),^{13,27} American Institute of Ultrasound in Medicine,^{24,29} World Federation of Ultrasound in Medicine and Biology,^{25,28} and National Institutes of Health¹⁵ have included recommendations for bioeffects research in those areas where a paucity of information was available, which included the study of fundamental mechanisms leading to bioeffects and postnatal studies in experimental animals after in utero exposure. Most animal studies have provided limited information that can be applied to humans based on the methods incorporated for the exposures (output parameters, length of exposures) and the substantial differences physiologically in scanning a small laboratory rodent versus a confined area of an adult human. Studies with nonhuman primates³⁰ can provide more relevant data due to their reproductive and developmental similarities to humans and the ability to control the conditions of exposure (ie, number of examinations performed, time between each examination, stage of development, duration of exposure, length of time the beam is concentrated in a given area, output parameters of the ultrasound unit) so they more accurately simulate the human clinical setting.

One of the most central issues regarding bioeffects has been quantitation of the "dose" that the embryo/fetus receives during an ultrasound examination. This has become a monumental task based on the multitude of parameters that must be considered when attempting its assessment. Examples include factors related to attenuation (reported in decibels [dB])¹²⁴ and the volume of tissue that must be traversed before the beam reaches the conceptus. The in utero ultrasonic intensities in both the gravid and nongravid human uterus have been estimated by mathematical techniques based on these variable tissue layers.^{10,13,38} In early studies, layers between the skin surface and gestational sac (ie, muscle, fat, peritoneum, urinary bladder) yielded a total attenuation in the range of 2 to 20 dB at scanning frequencies of 2 to 5 MHz. The distances between the abdominal surface and the conceptus in early pregnancy were estimated to range between 2 to 11 cm. In later studies, similar distances were estimated to be in the range of 2.6 cm¹¹⁸ while others reported ranges from 4.4 to 12 cm.³⁸ Direct in utero intensity measurements have been obtained in the human female; the average attenuation was reported to be 6.2 ± 3.5 dB under full and 7.3 ± 4.9 dB under empty bladder conditions in the nongravid uterus^{120,121} and 7.2 ± 3.7 dB under full and 9.3 ± 6.0 dB under empty bladder conditions in the gravid uterus.³⁸

Further studies have applied the *fixed-path attenuation*

tissue model^{27,38,119,121} where attenuation is based on the assumptions that the ultrasonic attenuation between the skin surface and conceptus is linearly dependent on frequency and independent of distance. Here, the fixed-path attenuation coefficient has been estimated experimentally to be 3.6 ± 2.2 dB/MHz and could be applied independent of bladder state (full versus empty), gestational age (between 7 and 20 weeks), and distance between skin surface and conceptus (between 4.4 and 12 cm).³⁸ The NCRPM²⁷ has recommended the use of the fixed-path attenuation coefficient values of 1.0 and 0.75 dB/MHz for first and second trimester obstetric applications, respectively. These values are based on a worst-case ("maximum" exposure) approach but are not consistent with the experimental observations.^{38,121}

The *overlying tissue model*^{38,120-122} is based on the assumptions that the ultrasonic attenuation occurs uniformly within intact tissue *only* and that there is negligible attenuation from any intervening fluid path. The overlying attenuation coefficient has been experimentally estimated to be 0.82 ± 0.54 dB/cm-MHz and could be applied independent of gestational age (between 7 and 20 weeks); however, it is dependent on bladder state and distance between skin surface and conceptus (between 4.4 and 12 cm).³⁸

The FDA's Center for Devices and Radiological Health uses the *homogeneous tissue model*^{27,35,36,38} where attenuation is based on the assumption that the ultrasonic attenuation occurs uniformly over the total distance between the skin surface and the conceptus. The homogeneous attenuation coefficient has been experimentally estimated to be 0.52 ± 0.33 dB/cm-MHz and could be applied independent of gestational age (between 7 and 20 weeks) and empty bladder state; however, it is dependent on distance between skin surface and conceptus for the full bladder state (between 4.4 and 12 cm).³⁸ The FDA^{35,36} uses a value of 0.3 dB/cm-MHz as a factor for manufacturers in their 510(k) process (required for all ultrasound systems approved for marketing). Since the measured values for the tissue models already noted are considerably greater than the values used by the FDA, it is apparent that the output requirements for ultrasound systems err on the side of safety. It is evident, however, that improved methods for estimating the attenuation that occurs in vivo will be required in order to more accurately assess the dose received by the second and third trimester fetus. This information will also help to confirm that the attenuation coefficient used by the FDA continues to remain relevant.

EPIDEMIOLOGIC STUDIES

Human epidemiologic studies¹²⁵⁻¹³³ and numerous in vivo studies in mammals have been performed in an effort to examine the many issues related to the use of diagnostic ultra-

sound in regard to safety. Overall, some conclusions can be drawn from these reports. For one, if ultrasound were a physical agent capable of inducing gross malformations, then a rise in the occurrence of birth defects would have been documented by now. This has not been the case, as epidemiologic studies have shown no correlations between a rise in its use and the incidence of congenital anomalies. Based on the fact that results of experimental studies have proven inconsistent, however, it is clear that the interaction of ultrasound with biologic systems, particularly those with rapidly dividing cells, is still not fully understood. What remains of concern are the subtle or long-term manifestations, or both, of frequent intrauterine exposure. These concerns remain pertinent due to a number of factors, such as the continued rise in the percentage of the prenatal population that is exposed each year and advances in technology that can result in increased exposure (dose) to the fetus. The exposure time may also be increased as additional diagnostic information is sought. These points emphasize the need to pursue these questions in an effort to confirm that unwanted effects do not occur.

Although an increase in dyslexic children among those exposed to ultrasound in utero has been reported,¹³⁰ no differences between groups were observed in multiple neurologic and cognitive tests performed at 7 to 12 years of age. Other studies¹²⁶ have failed to confirm any significant effects related to exposure wherein no significant differences in head circumference at birth or in height and weight from birth to 6 years of age between 149 human sibling pairs of which only one was exposed to ultrasound prenatally. Prior studies that have suggested the occurrence of growth retardation in the human population after exposure to ultrasound prenatally^{127,130,132} may have been confounded by the population of infants incorporated in the analyses. It has also been suggested¹²⁷ that a relationship may exist between the frequency of ultrasound exposure and reduced body weights (ie, maternal and fetal risk factors rather than the ultrasound exposure may be the primary cause of the low body weights observed postnatally).

Also reported¹³⁴ was an increased rate of intrauterine growth restriction in fetuses serially exposed to clinical ultrasound studies from 18 to 38 weeks' gestation (average of five examinations including placental arcuate and umbilical artery Doppler flow studies). Although these results are subject to significant criticism, fetal weight restriction as a result of ultrasound exposure has previously been reported in several animal models.³⁰ Thus, this is an area that requires continued attention given the conflicting epidemiologic data.

OUTPUT DISPLAY STANDARD

The purpose of the Output Display Standard³² is to provide the capability for users of diagnostic ultrasound equipment

to operate their systems at levels much higher than previously possible in order to have greater diagnostic capabilities. In doing so, the possibility exists for the potential to do harm to the patient. Thus, it becomes imperative to provide to the system user a means for assessing the system's output and specifically a means for assessing the biologic consequences of that increased output. The Output Display Standard³² does this, in part, by providing calculated quantities that are based on biophysical indicators, that is an index that relates to the maximum tissue temperature increase in the beam (the thermal index) and an index that relates to the potential for producing cavitation (the mechanical index). Therefore, these two biophysical indices are provided so that the equipment operator has real-time information available to make appropriate clinical decisions (ie, benefit versus risk) and to implement the "as low as reasonably achievable" (ALARA) principle.

Thermal Indices

Table 2-2 describes the three thermal indices for three different tissue models and two scan mode conditions. They are termed, along with their abbreviations, as follows:

- TIS: Soft tissue thermal index
- TIB: Bone thermal index
- TIC: Cranial bone thermal index

The basic definition of all thermal indices is

$$TI = \frac{W_0}{W_{DEG}} \quad [1]$$

where W_0 is the source power of the diagnostic ultrasound system and W_{DEG} is the source power required to increase the tissue temperature 1°C under very specific and conservative conditions. Tissue perfusion was included in the development of the W_{DEG} expressions.

Tissue Models and Scanning Modes

Three tissue models were considered (see Figs. 2-3 to 2-5). Figure 2-3 is typical of a scanning condition in which there is only soft tissue in the sound beam path. The assumption is that the soft tissue is homogeneous (in terms of both acoustic and thermal properties) with an attenuation coefficient

TABLE 2-2. OUTLINE OF THE THREE THERMAL INDICES OF THE OUTPUT DISPLAY STANDARD

	Scanned Mode	Unscanned Mode
Soft tissue	TIS at surface	TIS: small aperture, large aperture
Bone at focus	TIS at surface	TIB
Bone at surface	TIC	TIC

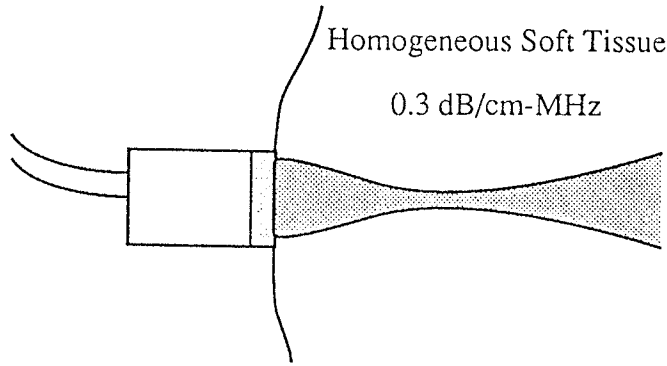


Figure 2-3. Homogeneous soft tissue model.

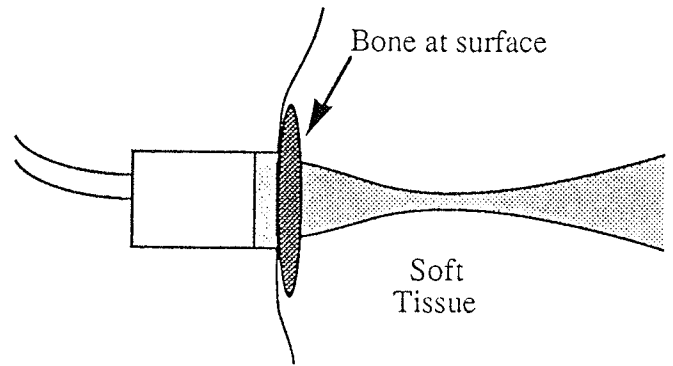


Figure 2-5. Bone at surface tissue model.

cient (also referred to as a derating factor) of 0.3 dB/cm-MHz.

Figures 2-4 and 2-5 consider two cases in which bone is within the sound beam path. The bone at focus tissue model is typical of second and third trimester fetal imaging in which fetal bone may be intercepted by the sound beam (see Fig. 2-4). Here, the interposed tissue is assumed to have the same homogeneous properties as the soft tissue model. The bone at surface tissue model is typical of adult cephalic imaging (see Fig. 2-5).

Both scanned and unscanned modes are considered in the development of the W_{DEG} expressions for the estimate of the appropriate thermal indices (see Fig. 2-6).

Soft Tissue Thermal Index at Surface

Figure 2-7 shows a typical axial temperature increase profile for the homogeneous soft tissue model under scanned mode conditions. Note that the maximum temperature increase occurs near the surface, usually within the first couple of centimeters of the skin surface.

Figure 2-8 shows a typical axial temperature increase profile for the bone at focus tissue model under scanned mode conditions. Note that the maximum temperature in-

crease also occurs near the surface, usually within the first couple of centimeters of the skin surface. The same TIS calculation is made for both conditions shown in Figures 2-7 and 2-8. The TIS calculation estimates the thermal index at the location where the temperature increase is a maximum value (ie, at the surface).

Cranial Bone Thermal Index

Figure 2-9 shows a typical axial temperature increase profile for the bone at surface tissue model under scanned mode conditions. Note that the maximum temperature increase occurs at the bone surface. Figure 2-10 shows a typical axial temperature increase profile for the bone at surface tissue model under unscanned mode conditions. Note that the maximum temperature increase also occurs at the bone surface. The same TIC calculation is made for both conditions shown in Figures 2-9 and 2-10. The TIC calculation estimates the thermal index at the location where the temperature increase is a maximum value (ie, at the adult cranial bone surface).

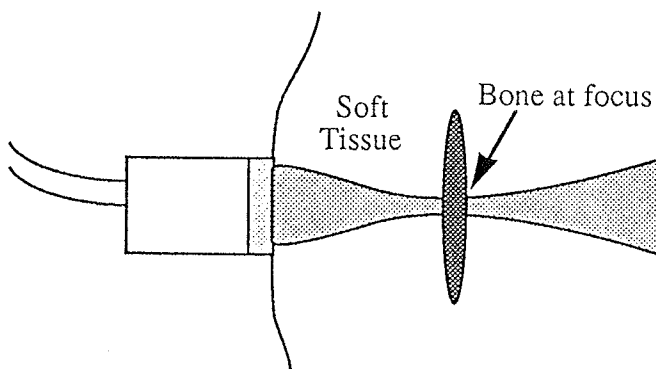


Figure 2-4. Bone at focus tissue model.

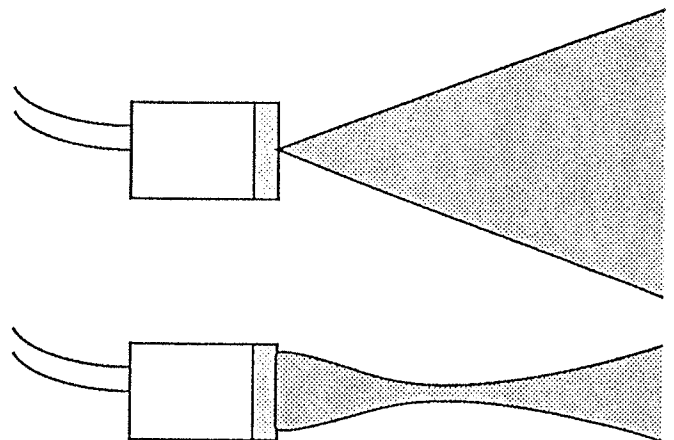


Figure 2-6. Scanned (top) and unscanned (bottom) modes.

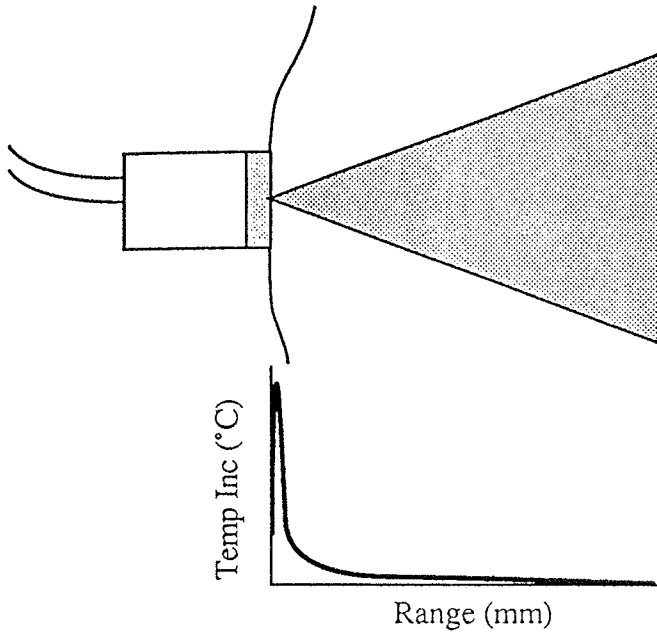


Figure 2-7. Axial temperature increase profile for the homogeneous soft tissue model and scanned mode.

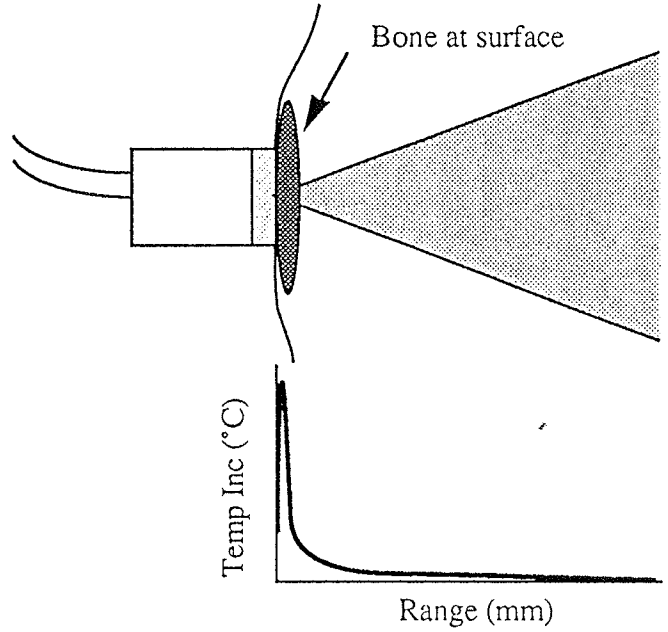


Figure 2-9. Axial temperature increase profile for the bone at surface tissue model and scanned mode.

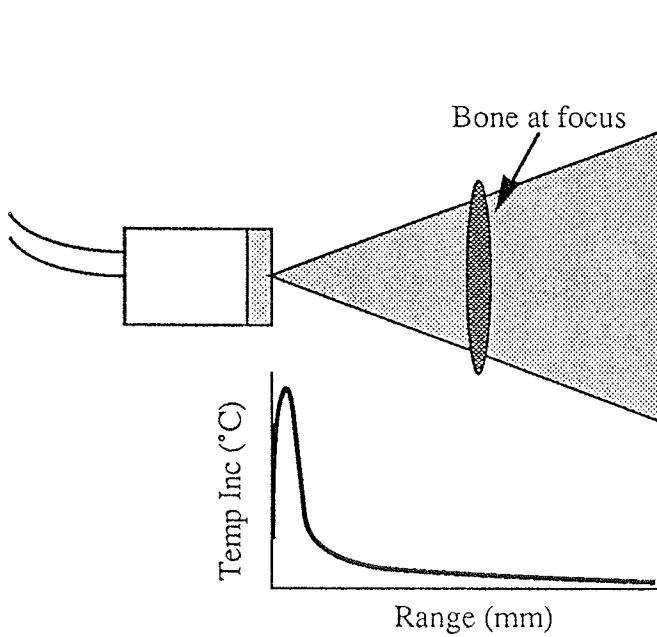


Figure 2-8. Axial temperature increase profile for the bone at focus tissue model and scanned mode.

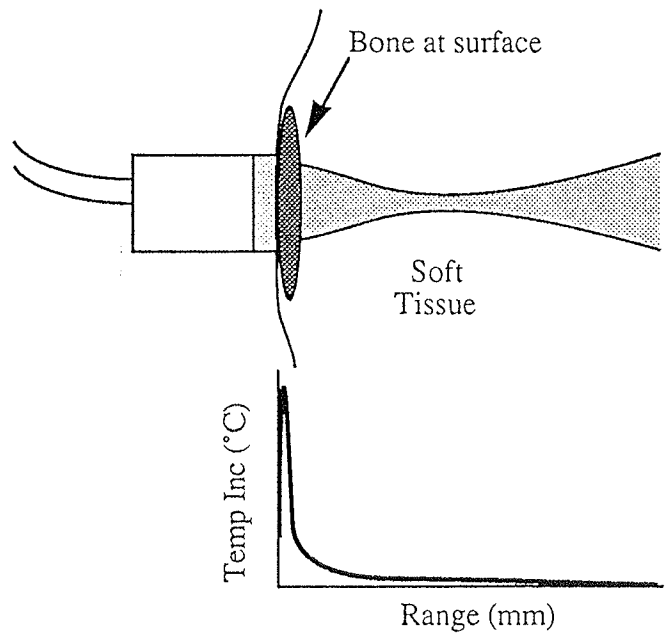


Figure 2-10. Axial temperature increase profile for the bone at surface tissue model and unscanned mode.

Bone Thermal Index

Figure 2-11 shows a typical axial temperature increase profile for the bone at focus tissue model under unscanned mode conditions. Note that the maximum temperature increase occurs at the bone, not at the skin surface, although there is an increase in temperature there also. The TIB calculation estimates the thermal index at the location where the temperature increase is a maximum value (ie, at the second or third trimester fetal bone).

Soft Tissue Thermal Index: Small and Large Apertures

Figure 2-12 shows typical axial temperature increase profiles for the homogeneous soft tissue model under unscanned mode conditions. The axial temperature increase profile is slightly different depending on the size of the transducer aperture. If the aperture is large (active aperture area $>1 \text{ cm}^2$), then the maximum temperature increase occurs near, but not at, the surface, usually within the first couple of centimeters. On the other hand, if the aperture is small (active aperture area $\leq 1 \text{ cm}^2$), then the maximum temperature increase occurs at the surface. Two separate calculations of TIS are made and displayed to estimate the thermal index at the appropriate location where the temperature increase is a maximum value. The diagnostic ultrasound system knows which transducer is in use and makes the appropriate calculation internally.

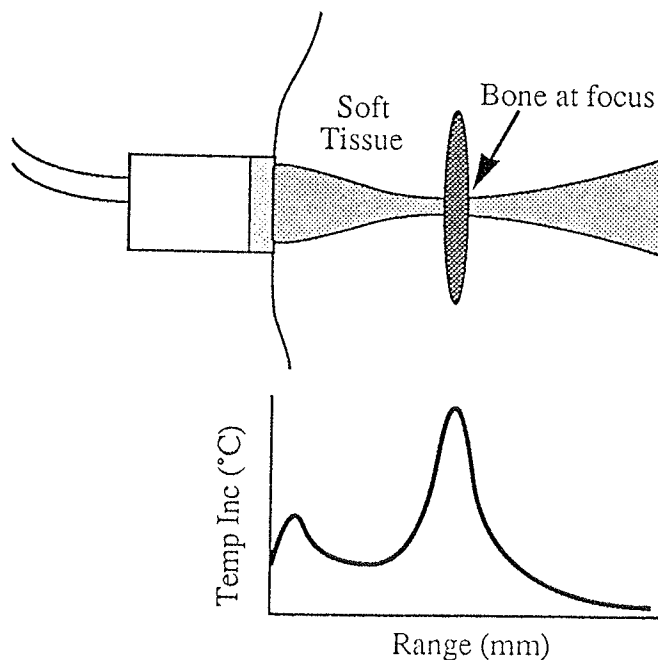


Figure 2-11. Axial temperature increase profile for the bone at focus tissue model and unscanned mode.

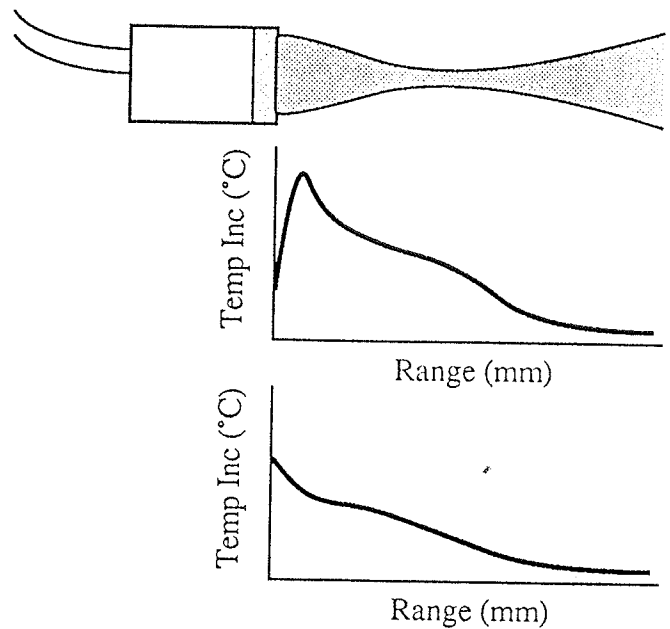


Figure 2-12. Axial temperature increase profiles for homogeneous soft tissue model and unscanned mode (top: large aperture; bottom: small aperture).

Mechanical Index

The mechanical index (MI) is defined as

$$MI = \frac{p_{r,3}}{\sqrt{f}} \quad [2]$$

where $p_{r,3}$ is the derated peak rarefactional pressure (see Fig. 2-13) in megapascals (MPa) and f is the ultrasonic frequency in MHz. The derating factor (attenuation coefficient of homogeneous soft tissue model; see Fig. 2-3) is assumed to be 0.3 dB/cm-MHz. The MI represents the potential for cavitation in tissue, although there has never been a reported case where cavitation has been known to occur from scanning a patient with diagnostic ultrasound equipment. The index is based on theoretical and laboratory experiments.

Display Requirements

If the diagnostic ultrasound equipment is capable of equaling or exceeding a TI of 1, then the appropriate TI (TIS, TIC, TIB) must be displayed in increments of no more than 0.2 for indices less than 1 and in increments of 1 or less for indices equal to or greater than 1.

If the diagnostic ultrasound equipment is capable of equaling or exceeding an MI of 1, then the appropriate MI must be displayed in increments of no more than 0.2 for indices less than 1 and in increments of 1 or less for indices equal to or greater than 1.

In those cases where indices must be displayed, the index must be displayed from a value of 0.4. This allows

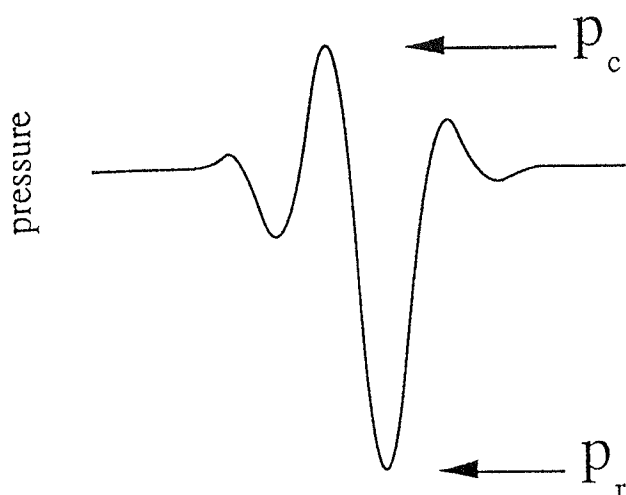


Figure 2-13. Typical acoustic pressure waveform that shows the peak compressional pressure (p_c) and peak rarefactional pressure (p_r).

the system operator to know when the appropriate index is approaching a critical value, say, around 1, and then to make the appropriate clinical decision.

All indices do not have to be displayed at the same time.

- The MI need only be displayed when the system is operating in B-mode imaging only.
- The TIS and TIB need not be displayed at the same time during an obstetric examination but the system must have the capability for the operator to choose between the two indices to be displayed.
- The TIC must be provided when the system is intended solely for adult cephalic application.

The system must also have the capability to display the appropriate indices under combined modes of operation. This applies to the thermal indices where multiple modes of operation can produce a summation of heating from each mode.

SUMMARY

The scanning conditions and information available suggest that the perceived risk associated with the clinical use of ultrasound is low, provided that the length of the examination period and methods used for scanning pregnant patients are "prudent."^{29,131} It must be emphasized, however, that, as discussed earlier, our knowledge regarding ultrasonic bioeffects and biophysical interactions with developing tissues is incomplete at this time. Several areas will require more rigorous investigations with appropriate animal models. Because of this apparent paradox, it is essential for clinicians

and sonographers to be aware of the most up-to-date information on any perceived risks so that they can continue to render an informed benefit-risk judgment. The principal source of such data will be from relevant animal experimentation that can focus on defined effects and the respective mechanisms responsible for their occurrence.

ACKNOWLEDGMENTS

The author gratefully acknowledges the partial support by a grant from the National Institutes of Health's National Cancer Institute (CA 09067) and the National Institute of Child Health and Health Development (HD 21687).

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