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Acoustic Bioeffects: A Primer

Ultrasound is used widely in medicine as both a diagnostic and therapeutic tool. Through several physical mechanisms, ultrasound produces a variety of biological effects in human tissues *in vitro* (in the laboratory) and *in vivo* (in the living organism).[1] Usually these mechanisms are viewed as the potentially negative aspect associated with insonating the human body, and certainly, some tissue changes have been reported in laboratory controlled experiments following exposures at intensities within the diagnostic range.[2] However, in the past several years, creative researchers have developed methods that use these predictable biophysical mechanisms as the foundation for emerging medical therapies and in industrial pharmacological applications.

Review and Definitions

Sounds waves carry energy from one place to another as packets of particle compressions and relaxations (rarefactions). Much like a spring that is compressed, energy is stored in the areas of compression in a sound wave; areas of rarefaction represent the rebound to a state of equilibrium sometimes stretching particles farther apart before springing back to their normal position. As acoustic energies propagate through living tissue, this energy is dissipated by several mechanisms referred to collectively as attenuation. The primary method of acoustic energy dissipation is its conversion into heat, in fact; approximately 80% of the energy that is attenuated is converted into heat by the process of absorption. Absorption is primarily the result of inertial and frictional forces encountered by the ultrasound pulse. The other 20% of energy is lost through other attenuative processes such as reflection and scattering.[3]

The first law of conservation of energy states that energy can neither be created nor destroyed, but it can be converted from one form to another. The introduction of acoustic energies into human tissue, as occurs during diagnostic and therapeutic ultrasound procedures follows the economy of this law. Accordingly, the mechanical energy in an ultrasound pulse does not simply disappear as it propagates through human soft tissue; it is dissipated by a variety of mechanisms, which can induce changes on a cellular and subcellular level. These changes are referred to as ***bioeffects****.* There are two categories of ultrasound bioeffects: ***thermal*** and ***nonthermal.*** Thermal bioeffects are those produced from increases in temperature in the tissue being insonated as the mechanical energy of the ultrasound is dissipated primarily in the form of heat. Nonthermal bioeffects, a group of less well understood mechanical interactions between ultrasound energies and human tissue, are those caused by the motion of tissue particles as compression/rarefaction waves travel through tissue. The most commonly studied types of nonthermal bioeffects include: cavitation, streaming, and free radical production.

Thermal Bioeffects

Changes in living tissue that results from temperature increases are called thermal bioeffects. In the realm of ultrasound physics, temperature increases are caused by the absorption of acoustic energy in body tissues. If the rate of heat deposition in a particular area exceeds the body's ability to dissipate in the heat, tissue temperatures rise (hyperthermia).[4] The elevation of tissue temperatures during typical 2-D diagnostic examinations using pulsed-echo imaging techniques is usually quite small and well within accepted safety levels, however, it does occur.

Several conditions found in the human body can actually enhance thermal bioeffects. The presence of bone in the focal zone with its associated increased attenuation levels has been shown to induce heating in the adjacent soft tissues.[5] Also, minimal vascular perfusion in some types of tissue (such as embryonic or ischemic tissue) diminishes the ability of heat dissipation via the circulatory system. Another variable in considering the thermal effects of tissue insonation is the well-documented increase in tissue attenuation due to core tissue temperature. Elevation of the body temperature above 37^{o}C produces an increase in attenuation and absorption of acoustic energy presumably as the result of changes in tissue composition.[6] [7] Since hyperthermia is a recognized teratogen in mammalian laboratory animals and is a suspected teratogen for humans, the potential for thermal bioeffects in the human body is very real.[8]

The threshold temperature elevation for hyperthermia-induced teratogenic effects in experimental mammals is estimated to be approximately 1.5°C above normal core values. These changes are observed in the laboratory with ultrasonic exposures of long duration, typically with exposure times of approximately 5 minutes or more. Bacon and Carstensen demonstrated in a laboratory model designed to mimic the sonographic scanning of a fetus through a full urinary bladder a three-fold increase in the temperature of the insonated tissue. In their experiment, they used an ultrasound beam with a constant spatial-peak-temporal average (SPTA) of $1W/cm^2$ and demonstrated a maximum temperature rise of 2^{o}C.[9] While this level of tissue temperature increase would be unlikely to occur during routine diagnostic ultrasound examinations, the capability for achieving this level of acoustic exposure is within the capability of some modern diagnostic ultrasound devices sold within the USA and abroad.[10]

Nonthermal Bioeffects

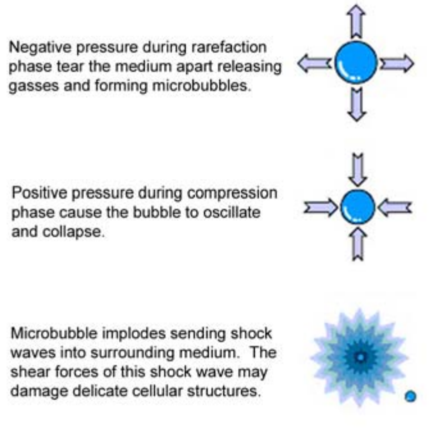
That sound waves have mechanical, nonthermal effects on human tissue is without dispute. In fact, in recent years, several therapeutic applications of ultrasound have relied on these principles for their efficacy. High intensity focused ultrasound (HIFU) has been used to induce coagulative necrosis in the prostate in men with benign prostatic hypertrophy and prostate cancer in an attempt to eradicate the pathology.[11] [12] Extracorporeal shockwave lithotripsy

(ESWL) has become a well-established therapeutic modality in the treatment on kidney stones and other types of urological pathology, such as Peyronie's disease.[13] [14] These, and other examples of practical applications of nonthermal bioeffects, will be considered in depth later.

Both of the above examples, of course, utilize acoustic energies with exponentially greater power than that which is used in diagnostic imaging. Still, the physical principles remain the same: localized areas of increased pressure followed by areas of rarefaction push and pull on tissue particles. If the "pushing" contains enough energy it can smash particles together with tremendous force. Conversely, the "pulling" on particles during the rarefactory phase of a wave can rip particles apart with enough force to cause them to implode (cavitation). The transfer of energy by the loss of forward momentum of an acoustic wave can also initiate a process called "acoustic streaming" in which flow currents are induced in the medium. Each of these nonthermal bioeffects, cavitation and acoustic streaming, will be considered separately. [15]

Cavitation

Figure 1. Acoustic Cavitation



Negative pressure during rarefaction phase tear the medium apart releasing gasses and forming microbubbles.

Positive pressure during compression phase cause the bubble to oscillate and collapse.

Microbubble implodes sending shock waves into surrounding medium. The shear forces of this shock wave may damage delicate cellular structures.

Cavitation is the process by which "cavities" are formed in non-elastic media, such as water and human tissue, as acoustic pressure waves propagate through. When the amplitude of an ultrasound beam reaches certain threshold levels, the magnitude of the negative pressure in the areas of rarefaction becomes sufficient to tear the medium apart, causing the liquid to fracture allowing gasses present within the medium to escape. Small "cavities" or microbubbles form and, under the constant bombardment of subsequent positive pressure waves, begin to oscillate. These microbubbles ultimately collapse, or implode, violently, sending shock waves into adjacent parts of the medium. [16] [17] (Figure 1.) These shock waves can damage adjacent cells in a variety of ways.[18] The process of cavitation has been shown in both *in vivo* and *in vitro* studies to cause a variety of bioeffects on multiple histological levels: ***tissue, cellular, subcellular,*** and ***molecular.***

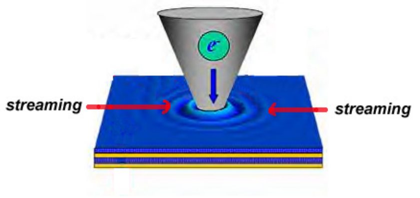
On the ***tissue*** level, studies have consistently demonstrated that cavitational effects of acoustic energy can cause hemolysis, the disintegration of blood cells, particularly when sonographic contrast agents are present.[19] [20] Cavitation is also believed to be the mechanism responsible for tissue damage in the central nervous system, embryonic and fetal tissue, and the petechial hemorrhages found in the small intestines and lung of laboratory animals exposed to varying levels of acoustic energy.[21] Each of these tissue-specific bioeffects is considered below some of which have clinical ramifications particularly in the realm of contrast-enhanced echocardiography.

On the ***cellular*** level, cavitation bubbles have been shown to induce cell death or transient changes in the permeability of cell membranes.[22] [23] Cavitation can also induce changes on a ***subcellular*** level, causing degeneration and shrinking of a cell nucleus and clumping of the chromosomes (pyknosis).[24] And on a ***molecular*** level, exposure to continuous insonation has been shown to cause breaks in DNA strands in rat ovary cells, presumably due to cavitational effects.[25] Certainly, when these changes are considered collateral damage to diagnostic applications of medical ultrasound, they are undesirable and form the traditional premises of concern over the safety and appropriate usage of diagnostic acoustic ultrasound devices and. However, as will be discussed below, when these bioeffects are harnessed and used in precise acoustic instruments, they can form the foundation for several exciting new therapeutic and pharmacological methods.

Acoustic Streaming

Acoustic streaming is a phenomenon characterized by unidirectional flow currents in a fluid due to the introduction of sound waves. In the human organism fluid-flowing conduits that are germane to a consideration of bioeffects include primarily the include arteries, veins, blood and fluid collections, and intracardiac circulation. When ultrasound energy passes into a fluid collection, it applies a force to the fluid through the fluid-mechanics process known as *momentum transfer*. Simply stated, the vibrational forces of the ultrasound beam enhance the flow energy already present in the medium. A streaming within the fluid results that is a function of the acoustic intensity, velocity of sound, and the attenuation characteristics of the medium.[26] (Figure 2.)

Figure 2 **Momentum Transfer**



A good example of the mechanism of acoustic streaming can be found in some cutting-edge cleaning instruments used by endodontists. By advancing a precision instrument into the root canals of teeth, ultrasound energy can be introduced that actually mechanically debrides the root surface. (Figure 3.)

Figure 3. **Acoustic Streaming**

There is little evidence to support the occurrence of any adverse biological effects attributable to acoustic streaming, at least from exposure to the energies employed in diagnostic ultrasound instruments. The concern for potential tissue damage that may occur *in situ* lies with the production of sheer stresses, particularly near the focal zone of a transducer where the intensity of the beam is greatest which may lead to damage of the cell membrane and ultimate cell lysis.[27] [28] There is little evidence in the literature, however to support this in either *in vitro* or *in vivo* studies. On the contrary, several studies have shown, that acoustic streaming actually may **reduce** the temperature rise generated by ultrasound at the surface of bone. Wu and Winkler demonstrated in 1994 that a bone surface covered by a 1 mm layer of soft tissue experiences a substantially lower temperature rise (60%) than a similar interface without a soft tissue layer.[29] The suggestion is that the microstreams produced by momentum transfer and other acoustic physical phenomena conduct heat away from the bone reducing the thermal effects.

There are other potential benefits of acoustic streaming in diagnostic applications. Since attenuation characteristics of the medium (viscosity) directly affect the production of microstreams and, since microstreams create movement within fluid collections, one could presumably identify these streams using sensitive color and power Doppler imaging modalities when assessing fluid (cystic) collections in the body.[30] Several interesting studies have been done demonstrating the feasibility of this application. For example, evaluation of different types of ovarian cystic masses have concluded that endometriomas do not demonstrated acoustic streaming while cystadenomas do (within a defined range) permitting confident exclusion of endometrioma as a diagnosis if a cyst shows acoustic streaming.[31] [32] Nightingale, et al, have successfully used acoustic streaming to differentiate small, possibly newer, breast cysts from solid masses that were not discriminated on conventional sonography.[33] [34] Acoustic streaming may also be a valuable tool for enhancing the distinction between liquid blood and thrombosis. This distinction can sometimes be difficult with conventional sonography but has high value in managing trauma patients with internal hemorrhage. In studies done by Shi, et al, the presence of acoustic streaming in blood decreased as the blood began to clot and streaming was not detected in clotted blood[35] [36]

Acoustic Indices

In an effort to standardize discussion and analysis of the acoustic output of medical ultrasound systems, several acoustic indices have been developed. They provide a common ground upon which the actual *in vivo* effects of insonating human soft tissue can be studied and compared.

Thermal Index (TI)

The thermal index provides a method of quantifying the potential for ultrasonic heating of human tissue.[37] Because of the immense variety of types of tissue interfaces found in the human body, particularly when bone lies in the path of the beam, three specific types of thermal indices have been devised to provide simplified averages for heating potential. They are: soft-tissue thermal index (TIS), bone thermal index (TIB), and cranial bone thermal index (TIC). Each is designed to more closely approximate the energy deposition and temperature increases associated with scanning in various anatomical locations.

Generally speaking, the TI is the ratio of the ultrasonic power emitted by the transducer to the ultrasonic power required to raise tissue temperature by 1 °C for the exposure conditions being evaluated. While a complete exposition of the mathematics associated with calculation of the TI is beyond the scope of this paper, it can be stated as:

$$TI = \frac{W_o}{W_{deg}}$$

Where: W_O = output power of the transducer (Watts)
W_{deg} = power necessary to raise tissue temperature 1^oC[38]

In the calculation of all thermal indices, the average ultrasound attenuation in the body is assumed to be 0.3 dB/cm-MHz along the beam axis.[39] Obviously, then, higher frequency beams result in higher energy deposition (attenuation), a rule of thumb familiar to any sonography student. A study in 1999 by Egerton et al demonstrated that in addition to the fundamental frequency, significantly higher frequencies - present in a beam at high intensities - caused additional enhancement of the ultrasound heating.[40]

Clinical Implications

It is generally agreed that during the course of a routine sonographic examination there is negligible risk for thermal injury to the patient and that there is no justification to limit scanning for acceptable clinical indications, including ultrasound examination of normal pregnant women. If the TI does not exceed 1, currently available evidence indicates that the risk of an injury due to ultrasonic heating is negligible for the vast majority of diagnostic ultrasound examinations. [41] [42]

Mechanical Index

The mechanical index (MI) attempts to provide a measure of bioeffects related to the transfer of energy from propagating acoustic waves as they travel through human tissue.[43] As discussed above, the exact mechanisms by which cavitation and acoustic streaming occur are not well understood, however, the MI is an attempt to quantify these effects and to standardize the language used in predicting nonthermal biological effects in human tissues.[44]

The methods and assumptions used to calculate the MI are complex and beyond the scope of this paper. An excellent review of the mathematics associated with MI calculation can be found in a paper published by John Abbott in 1999.[45] The MI is the ratio of the largest peak rarefactional (relaxation) pressure in an ultrasound beam to a constant (C_{MI}).[46] Simply stated, it is a measurement of the negative acoustic pressure present in the insonated area. The constant (C_{MI}) has been defined in terms of Megapascals, a common metric unit of pressure or stress, so fundamentally, the MI is a ratio of the mechanical stresses found in tissue undergoing insonation. Another variable found in the MI formula, one that has practical implications is the frequency of the sound beam. It is inversely proportional to the MI; as frequency increases, the likelihood that mechanical effects will occur decreases.

$$\mathrm{MI} = \frac{P_r / f^{1/2}}{C_{MI}}$$

Where: P_r = peak rarefactional pressure
f = ultrasound frequency
C_{MI} = 1 MPa/ MHz

Clinical Implications

In general, MI numbers encountered in routine diagnostic ultrasound examinations are well below those necessary to induce nonthermal bioeffects. However, in *Guidelines for the Safe Use of Diagnostic Ultrasound* published by the federal agency Health Canada, studies are cited that have demonstrated a small risk of capillary hemorrhaging in the lung of neonates and infants undergoing ultrasound examinations if the MI exceeds 1.[47]

Relative MI values are also an important consideration in contrast echocardiography; lower MI values are associated with better imaging outcomes because there is less destruction of the microbubbles present in the contrast media.[48] *Absolute* MI values, however, do not predict degree of microbubble destruction as a wide range in bubble destruction at identical MI values has been observed.[49] Each of these specific implications is considered separately below.

Bioeffects in Specific Tissue Types

As mentioned throughout the course of this chapter, certain tissue types are more sensitive to the thermal and nonthermal mechanisms associated with insonating human tissues than others. Those most commonly mentioned in the literature include tissues of the central nervous system, lung and small intestine, and fetal/embryonic tissue.

Central Nervous System

Tissues of the central nervous system are particularly sensitive to damage by physical agents, such as heat and ultrasound. The use of Doppler ultrasound can cause significant heating of brain tissue because of the relatively high amplitudes needed to penetrate the bony calvarium when evaluating intracranial vasculature and the increased spatial and temporal intensities associated with pulsed Doppler imaging. This has significant implications for sensitive neural tissue such as that exposed during spectral Doppler flow studies of fetal cerebral vessels.

Barnet demonstrated in a study published in 2001 that pulsed, spectral Doppler ultrasound can produce biologically significant temperature increases in the fetal brain. As one would expect, the rate of heating near bone is highest, with approximately 75% of the maximum heating occurring within 30 seconds of insonation. Ultrasound-induced intracranial heating also increases with gestational age and the development and ossification of fetal bone. He also demonstrated that, unlike the quick dissipation of heat provided by active perfusion of soft tissue organs in adults, that blood flow has minimal cooling effect on ultrasound-induced heating of the brain when insonated with narrow focused beams used in clinical practice. The threshold for irreversible damage in the developing embryo and fetal brain is exceeded when a temperature increase of 4 degrees C is maintained for 5 min.[50] In another study on fetal guinea pigs published in 1998, Barnett's group demonstrated a mean temperature increases of 4.3^{o}C in brain tissue adjacent to the parietal bone and 1.1 ^{o}C in the mid-brain after 2-min exposures to pulsed Doppler ultrasound using clinically realistic intensity values. These temperature increases were lower (12%) than those obtained for ultrasound-induced heating near the bone in dead fetuses insonated in utero.[51] While no published reports in the literature demonstrate a clear causal relationship between *in utero* exposure to pulsed Doppler ultrasound, the lesson is clear – routine or unnecessary use of spectral Doppler in obstetrics is contraindicated.

Lung and Small Intestine

Gas-filled organs, such as the lung and small intestine, have demonstrated an increased susceptibility to ultrasound-induced bioeffects. The presence of air in these organs creates an interface that enhances bioeffects, particularly those related to inertial cavitation, however, thermal bioeffects also contribute to damage found in the tissue surrounding air pockets.[52] In studies done on mice, exposure of lung and small intestine to 15 minutes of B mode and color Doppler imaging intensities resulted in hemorrhagic changes in the parenchyma. Cellular and subcellular changes were also been reported, i.e., a reduction in mitotic changes and an increase in apoptotic bodies suggesting that ultrasound bioeffects may be more diverse than previously described.[53] Studies on rat lungs *in vivo* using 4.0MHZ imaging and color Doppler ultrasound further supported the contention that cavitation can induce tissue damage.[54]

While not demonstrated in humans, the potential problems associated with mechanical bioeffects in gas filled organs include ultrasonically induced capillary hemorrhaging in neonatal and pediatric lung if the tissue is exposed excessively, particularly for infants and especially preterm neonates. Similarly, the potential for ultrasonically induced capillary hemorrhaging of the intestinal wall is a concern in patients with submucosal gas collections and inhibited peristalsis.[55]

Embryonic/Fetal Tissue

Little has been reported in the medical literature on the bioeffects of high-frequency ultrasound exposure in human embryos and fetuses. Obvious ethical implications precluded the design of *in vivo* human studies. However, several experiments in other mammalian embryos suggest there are no significant or appreciable adverse effects from ultrasound energies used during routine imaging. In a recent study by Brown, et al., pregnant mice were exposed to

Doppler or B-mode US on different embryonic days during the period of organogenesis. The mice were assessed for six weeks postnatally and, when compared to a control group, demonstrated no significant difference in pup weight, body length or crown-rump length observed. These results suggest that similar exposures in the human embryo should not cause significant adverse bioeffects.[56]

On the other hand since there are documented variations in both tissue temperature (TI) and nonthermal mechanisms (MI) observed in studies of the central nervous system, prudent use of ultrasound in all trimesters of pregnancy becomes imperative. Exposure should be kept as low as reasonably achievable (ALARA) because of the potential for tissue heating. Higher energy deposition in tissue is of particular concern for pulsed Doppler, color flow, first trimester ultrasound with a long transvesical path (> 5 cm), second or third trimester exams when bone is in the focal zone, as well as when scanning tissue with minimal perfusion (embryonic) or in patients who are febrile.[57] A recent study by Eyal Sheiner, et al. the demonstrated that during routine obstetric ultrasound examination overall exposure rates were generally low with the MI and the TI <1.0 during all trimesters of pregnancy. A small group of patients in their study (3.5%) had elevated TI's (>1.0). These changes were brief and were observed during color Doppler examination.[58]

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