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RECENT DEVELOPMENTS IN THE IMAGE QUALITY OF MEDICAL ULTRASOUND SYSTEMS, BIOLOGICAL EFFECTS OF ULTRASOUND AND ITS PHYSICAL BASES.+

Ali ŞAHİN, Ph..D. *

In this paper, medical uses of ultrasound, recent developments on nonlinear propagation of ultrasonic waves in biological mediums were briefly investigated. Tissue damaging effects of nonlinear propagation of ultrasonic waves were discussed underlying the heating effect of the high intensity ultrasound. Problems related to the ultrasonic cavitation and streaming were investigated. Effects of nonlinear propagation on the ultrasonic image quality, basic physical problems related to the calibration of the ultrasonic medical equipments and their physical bases were also discussed.

***Key words**: Ultrasonics, image quality, physical bases.*

Tıbbi Ultrasonografi Sistemlerinin Görüntü Kalitesindeki Son gelişmeler, Ultrasonun Bio-Etkileri Ve Fiziksel Temeli

Bu çalışmada, ana hatlarıyla non-lineer ultrasonografideki son gelişmeler, non-lineer ultra ses dalgaların medikal amaçlarla kullanımı ve biyolojik ortamlarda yayılması incelendi. Yüksek genlikli non-lineer ultra ses dalgaların doku hasarı etkileri daha çok ısı etkisi dikkate alınarak tartışıldı. Ultrasonik kavitasyon ve streaming etkilerine dayalı fiziksel problemler incelendi. Lineer olmayan fiziksel olayların ultrasonik görüntü kalitesi üzerindeki etkileri ile ilgili problemlerin fiziksel temelleri tartışıldı.

***Anahtar kelimeler**: Ultrasonografi, görüntü kalitesi, fiziksel temelleri.*

Although problems in nonlinear ultrasonics have been pondered since the 18th century[1], practical applications of the ultrasonic waves have grown over the past few decades as the existence of the nonlinear effects has become more widely understood. More recently, the interest in nonlinear effects in medical ultrasound has grown considerable as the importance of such effects are more widely released. Today, ultrasound is an established tool in medical science, its uses ranging from diagnosis to therapy. In diagnosis, it is used, for example to locate renal tumors, breast tumors,

* Inonu University, Faculty of Science and Arts, Physics Department, MALATYA,TURKEY.

Correspondence address:
Doç.Dr. Ali ŞAHİN
İnönü Üniversitesi, Fen-Edebiyat Fakültesi
Fizik Bölümü, 44300-MALATYA.

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indicate retinal detachment and most commonly for obstrectic scanning[2]. In the later case, fetal maturity, diagnosis of early or multiple pregnancies, placental localisation, assessing utero-placental blood flow and monitoring fetal heart rate from the majority of its applications. In therapy, ultrasound is used either to promote healing of tissue[3] by heating or to destroy renal calculi using lithrotripsy[4]. In addition to this, work is now being done to treat cancer with the aid of ultrasound[5]. This follows two pronged approaches. Ultrasound can be used directly by destroying carcinorous cells or indirectly by acting as an enhancing agent with chemoterapic drugs.

The wide variety of uses has resulted in a range of devices being implored. For diagnostic applications high frequency (around MHz) short pulses are transmitted in order to achieve reasonable resolution in ultrasonic image quality. For therapeutic uses either longer pulses are used to produce heating or very short high pressure pulses (at hundreds of kilo Hz) are employed to disintegrate calculi[4] .

NONLINEAR PROPAGATION AND ITS CONSEQUENCES

As ultrasound like any wave is absorbed during its propagation in the body, consideration needs to be given to the transfer of energy in to the medium through which it is travelling.[6,7,8] This is especially relevant for biomedical applications where the pressures and frequencies employed result in nonlinear propagation through the medium. Distortion of outgoing ultrasonic waves results with the consequences that harmonics are produced which are attenuated at a faster rate. As high frequency ultrasound is used in many medical applications, a high particle velocity will add to the propagation velocity in a compressional half cycle and subtract from it during rarefraction. The result is that the wave peaks travel faster than the troughs, eventually the peaks catch up with the troughs and a shock wave is generated. The limiting case is like a sawtooth waveform, the distance at which occurs is called the shock formation distance.[9] This physical process is shown in Figure 1 and 2. In that case, some energy is transferred from the fundamental frequency to the higher harmonics and from harmonics to the body in the biological case. All these nonlinear physical processes have some effects on the tissue like biological, thermal, non-thermal and great effects on the ultrasonic image quality. The ultrasonic propagation path has also of importance on the image quality. Thus, all these effects need to be well understood by medical physist and doctors whose effectively use the medical equipment.

The physics of the biological effects of ultrasound: The result of harmonic generation and therefore extra deposition of energy into a biological medium requires consideration from the safety aspect of biomedical ultrasonics. There are two types of mechanism due to ultrasonic exposure that can be classified thermal and non-thermal. The type of mechanism involved in a particular case is determined by the state of the medium. In general, the interaction occurs at a molecular or macromolecular level in biological systems. This results in molecular vibrations and rotations. If the molecules are small and within a fluid environment, their mean particle velocities are large compared to the particle velocity imposed by the ultrasonic field. This causes relaxation processes to simply convert energy into heat. If however large mass molecules or less fluid media are considered (for example D.N.A) then their mean particle velocity is in the same order as that caused by the ultrasonic field, resulting in non-thermal effects. Both these mechanisms are enhanced by nonlinear propagation of the ultrasound beam which has been modeled by Şahin and Baker[8] and recently tested by Berg *et al*[10] with experimental results of Şahin[7], showing good agreement between theory and experiment.

Thermal Mechanism of ultrasound: The conversation of acoustic energy into heat is the result of relaxation and viscous processes. Both processes produce absorption of energy by causing the medium and the propagating wave to go out of phase. In water, which is a suitable medium for initial experiments, no relaxation occurs and absorption is governed by viscous losses, the result being that absorption is proportional to the frequency squared.[11] In biological tissue however, the frequency dependence of absorption is a little greater than unity. This implies that relaxation processes are also contributing to the absorption.

The extra absorption that is predicted by nonlinear propagation has been demonstrated by Muir and Carstensen[12], they presented nonlineairty induced absorption and the influence of these effects on the ultrasonic beam. Hynynen[13], using hypothermia beams, demonstrated in-vivo temperature rises. The effect of temperature elevation on tissue is either oblation of the cells or degradation of enzymes, however for this a rise of the order of ten degrees is required. The one exception to this is obstrectic scanning, where temperature rises of greater than 1.5 which are deemed to be hazardous[3]. The literature on experimentally observed temperature rises and their consequences is sparse. This is primarily due to the difficulty in performing such measurements and their interception, in other words the dependence on geometry and tissue type. Because of this, some work has been done to predict the temperature rises that are possible[14].. Most models are based on equations that have two terms, one that describes the energy source and one that describes the cooling mechanism. The cooling function consists of thermal conduction and perfusion. Thermal conduction can be modeled accurately but tissue perfusion is difficult because of the complex nature of the blood flow in a living system. At present these models suffer from the complex nature of the drawbacks due to the accuracy required. For example, a predicted temperature elevation of 1.5 is safe, however 2.0 is not, the accuracy being dependent on the input parameters relating to tissue characterisation. In addition to this, prediction also requires the inclusion of nonlinear effects, such as effective absorption.

Non-thermal mechanism of ultrasound: There exist a wide variety of non-thermal mechanisms associated with the ultrasound. However, cavitation and streaming are of importance to discuss.

Cavitation is a complex phenomenon, and has many definitions in the literature.[8,12,13,14,15] Broadly speaking it can be termed as the formation and activity of simple or complex bubble systems in the medium. There are generally two types of cavitation, stable and transient. With stable cavitation a bubble simply oscillates about an equilibrium radius in response to the pressure field generated by an ultrasonic wave. Transient cavities tend to oscillate nonlinearly, they expand to several times their mean radius then collapse. This collapse produces large temperatures and pressures which may be significant for safety considerations. Although transient cavitation is a nonlinear process it is not dependent on nonlinear propagation of the sound wave. The reason for this is that nonlinearly generated harmonics in the ultrasonic wave do not contribute significantly to the bubble oscillation. Indeed removal of energy from the fundamental frequency in a nonlinear wave may reduce the effect of cavitation. Although cavitation is not increased by nonlinear wave propagation it is nevertheless probably the most likely candidate for causing biological changes as cell lysine, membrane permeability and D.N.A degradation.

Acoustic streaming is referred to as bulk fluid movement[14,15].. It is the result of the attenuation of an acoustic wave, causing forces to be set in the fluid. In a linear system the acoustic variables (pressure, density, displacement) have time average values of zero. When second order terms are introduced into the equations of motions and state, the fluid element experiences both translational forces and torque which results in bulk fluid movement. The fluid velocity is spatially non-uniform, so produces velocity gradients. The effect of these gradients on objects within the streaming fluid is to subject them to large shear stresses. In biomedical situations this is potetionally hazardous. The verification of streaming in water has been demonstrated with great clarity by Strarritt *et al* [16], however its occurrence and effect in-vivo is not so clear. Because of this, there are few references in the literature. However, Ter Haar *et al* [17] irradiated 3 MHz ultrasound on the mouse uterus. After irradiation, membrane fragments were found and these were attributed to the shear stresses due to the streaming of blood plasma against the vessel wall.

Ultrasonic propagation path: Because of the complex nature of the human body, ultrasonic parameters show changes through the propagation path. This is particularly true in obstrectic scanning, where there can be several layers of different soft tissue and biological fluid between the transducer and the fetus, thus it results the interaction of ultrasound with the fetus. It is often postulated that a fluid path between the ultrasonic probe and the fetus could result in significant harmonic generation in the ultrasound field. These harmonics would then be quickly attenuated in the fetal tissue, so depositing energy in to the fetus. Thus it is clear that the various layers encountered by the beam also depend to a large degree on how the scan is taken. For example, if the bladder is full the beam passes through a volume of urine. The ultrasonic propagation path also depends on when the scan is taken during the pregnancy and also on the individual being scanned. For example, Duck and Perkins[18] performed a survey of tissue thickness and bladder depth for seventy for scans in the second trimester.

DISCUSSIONS

The effects of high intensity ultrasound on living tissue are not altogether clear, complex and dynamic nature of biological systems makes it difficult to perform experiments or make theoretical predictions. However on a microscopic scale, it is known that ultrasound can cause heating and a relatively small increase in temperature (6 °C) can cause damage in normal tissue particularly if the exposure is prolonged. The mammalian fetus is thought to be even more sensitive to elevated temperatures.[19] On a microscopic scale cavitation is probably an important effect since it can cause mechanical damage due to the violent collapse of cavitation bubbles and can also generate high reactive OH^- groups that may cause cell damage. In addition to the high tensile stresses that exist across a schocked wavefront could cause some mechanical damage.

The absence of clear mechanisms for biological damage at diagnostic levels of ultrasound and difficulty in characterising finite amplitude ultrasonic fields pose problems in defining a safe dose level for ultrasound since it is necessary to relate the level of the ultrasound field to the biological effects. The problem of biological effects was examined from an epidemiological wiev-point by Ziskin and Petiiti[20] and it was concluded that there was no evidence for advertise effects of ultrasound over a period of 25 years. But they did not preclude the possibility of subtle, long term or certain genetic defects which had so far escaped detection.

Although biomedical hazards caused by ultrasound exposure are important and need consideration, the accurate calibration of medical systems is of paramount importance. Unless the output field and source transducer parameters are known, any speculation of their affects are redundant. In order to calibrate the ultrasound field, a propagation medium is required, this is normally water under laboratory conditions. The reason is being; availability in large quantities, can be distilled, filtered and degassed, basic physical and chemical properties are known, and it is a universally standard medium. Water however does have its disadvantages as it is not a tissue-mimicking material, so the ultrasonic field in-vivo has to be inferred from water based measurements.

Standardisation on the type of measurements made also needs to be considered. Normally the parameters measured are in four categories; output power, pressure and intensity, acoustic beam shape and transducer characteristics. Under linear conditions determination of the ultrasonic field is not a great problem, as long as the calibrated detecting hydrophone does not have a resonance at the source frequency and its averaging effects are minimal. However under nonlinear conditions, simply measuring the amplitude of the fundamental do not characterise the ultrasound field. This is especially true in water where the harmonic generation is rich. Because of harmonic generation, the differences in frequency dependent absorption between water and tissue also cause problems for medical calibration.

Nonlinearity also causes problems in calibration of the detecting hydrophone because its frequency response is required. This is not linear and also encompasses the resonance frequency. Waveform distortion requires that consideration is given to the ultrasonic parameters that are being measured. For example, the peak positive pressure and the peak negative pressure are not equal, due to the nonlinearity in compression and expansion of a medium. This effects the image quality of the medical ultrasound systems in use and has to be well understood. In order to increase the image quality, the degree of the distortion of the ultrasonic wave has to be well known. In other words the nonlinearity parameter can be measured correctly. This could add an extra parameter to the information used for imaging but it is the most important factor for better resolution and imaging. In addition, if the harmonics are used for imaging then the better lateral resolution can be obtained due to well defined beam widths.

There is also a functional relationship between frequency and medium parameters such as attenuation and ultrasonic velocity but it has been studied to a limited extend in the literature. Work on characterisation of biological systems more accurately and over a larger frequency range still required. Nonlinear propagation of the ultrasonic wave can be utilised to perform these measurements. If a fully distorted wave ($\sigma = 3$ shock) is incident on a tissue or biological fluid sample, then the measurement of the waveform after traversing the sample will yield values for attenuation and sound velocity over a wide range frequencies.

CONCLUSIONS

The above discussion implies that much work still needs to be done in order to better characterisation for ultrasonic fields, biological effects and the ultrasonic image quality. The gaining of this type of knowledge will facilitate in the design of medical equipment and the understanding of the mechanisms of interaction with biological systems as nonlinear effects have significant implications for the designing of most types of medical ultrasound equipment. For example, acoustic saturation could limit the output of an imaging system so that increasing the drive level may simply increase the risk of biological damage without improving the performance. It may be possible to use the harmonics generated to improve the lateral resolution[21] to give quantitative measurements of tissue parameters.[22] The design of hypothermia systems could benefit from an accurate theoretical model for finite amplitude model for finite amplitude propagation in tissue since it would then be possible to predict the temperature rises generated in specific regions of the pressure field. The efficiency of lithotripters could also be improved if the nonlinear effects can be maximised to give the best chance of breaking stones. This might be done by modifying the model developed by Şahin[7] and Berg *et al*[10] and then extending it to clinically possible experimental situations. In conduction with this, experiments can be performed to measure the basic parameters as ultrasonic velocity, attenuation, and nonlinearity parameter which can then be fed into the mathematical model so that the predictions can be viewed with confidence. Although this approach is attractive, it does has disadvantages as the medical ultrasonic fields are generated at high frequencies and drive pressures. Any model that attempts to predict the fields needs to take into account nonlinearity, diffraction and attenuation effects. This implies that approximations need to be made which limit the accuracy so the quality of the image and range of the applicability of the model. In addition a relatively large computational time is required. The model implemented by Aanonsen[23] has been used by Baker[24] to predict ultrasonic pressure fields in water for a wide range of medically relevant situations, and has been found to agree well with experimental results obtained by the same author. Şahin[77]developed a theoretical model for a rectangular transducer geometry and presented experimental results in well agreement with the theory in most situations. The collaborative work between the groups in Norway[25], United Kingdom[26] and Turkey[27] has been revealed the most important factors for the best quality ultrasonic image, however still there is a need for the measurements performed in biological media and theoretical results in tissue like media. Thus the pressure field generated by medical scans can be determined and their consequences assessed.

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