THERAPEUTIC ULTRASOUND
Acoustic therapy using High Intensity Focused Ultrasound (HIFU) is making great progress in clinical applications, specifically in providing minimally-invasive treatment options. Today, HIFU therapy is being used to treat benign and malignant tumors with success rates unachieved by other modalities. Tumors of the prostate, liver, kidney, testis, bone, rectum, pancreas, breast, and uterus have been treated with HIFU, in some cases without anesthesia and on an outpatient basis. Furthermore, HIFU is being investigated for the first time in applications of hemostasis (arrest of hemorrhage). Abnormal blood vessels and actively-bleeding injured vessels can be treated, providing complete and lasting hemostasis. The greatest advantage of ultrasound is its ability to cause therapeutic action deep within the body, without causing damage to the surrounding normal tissue. This advantage is best exploited, and successful transcutaneous HIFU therapy implemented, when a robust imaging modality that provides real-time treatment guidance and monitoring, is integrated with HIFU. Magnetic Resonance Imaging (MRI), X-ray, and several ultrasound-based techniques are currently being investigated. These efforts are leading the way to a promising clinical realization of non-invasive image-guided acoustic therapy.

**INTRODUCTION**

The field of medicine is experiencing a remarkable change, in the form of a trend towards minimally-invasive and non-invasive therapy. Today, laparoscopic surgery, which uses only small incisions for insertion of surgical instruments, is increasingly chosen over traditional open surgeries. For example, solid abdominal tumors that were once excised using the traditional open-abdomen surgery are now treated using laparoscopic techniques. In emergency medicine, conservative non-operative management of solid organ injuries in trauma patients who are hemodynamically stable is becoming the standard of care. These minimally-invasive approaches, when compared to open surgeries, offer the advantages of reducing surgery time, the tissue damage associated with surgery, as well as transfusion requirements and its associated infection risks. The result is a shorter recovery time and hospital stay, reduced cost of health care, and generally a superior therapeutic outcome. Acoustic therapy has the potential to advance the field of minimally-invasive surgery one step further, where even small incisions will not be required to perform the operation. The surgery would be performed extracorporeally.

**ACOUSTIC THERAPY**

The hallmark of acoustic therapy is its ability to induce a biological effect (bioeffect) deep within the body without surgical intervention. Ultrasound waves can propagate through biological soft tissues and be brought to a millimeter-size focus to achieve a HIFU beam (Fig. 1).

**MECHANISMS OF THERAPY**

A focused wave attains a higher intensity than a collimated or diverging beam. In HIFU, both strong focusing (100-1000 gain in cross sectional area of the beam), and high power (100-1000 Watts) are used to induce a high intensity acoustic field in the focal region. Thermal and mechanical mechanisms are principally responsible for the therapeutic effects. The thermal effect results in a rapid increase in tissue temperature to values above the protein denaturization
temperature (~ 43 °C), that is, in the range of 70 °C to 100 °C, leading to coagulative necrosis of tissue.

A variety of mechanical effects are involved in acoustic therapy, including radiation pressure, acoustic streaming, and cavitation. The main mechanism of interest appear to be tissue disruption brought about by high-amplitude pressure oscillations. The outcome is rupture of cell and nuclear membranes, resulting in tissue death.

**GUIDANCE AND MONITORING OF ACOUSTIC THERAPY**

Guidance and monitoring of acoustic therapy is of utmost importance for clinical acceptance of this modality. Methods currently in use and under investigation include visual, X-ray, Magnetic Resonance Imaging (MRI), and ultrasound.

The most elementary method of guidance and monitoring is visual. X-ray imaging was the earliest imaging modality employed for guidance of HIFU therapy, for mapping the area of treatment and subsequently monitor the HIFU lesions. Magnetic Resonance Imaging (MRI) is a relatively new method of guidance for acoustic therapy. MRI provides the capability to characterize functional and physiological parameters of tissues, including diffusion, perfusion, flow and temperature. This latter capability is particularly useful in HIFU therapy, since it can be used to detect tissue damage induced by thermal ablation. However, high costs are associated with MRI; it requires a special environment that can hinder patient accessibility, and minimal use of metal parts in the HIFU assembly is necessary to prevent distortion of the MRI images.

Ultrasound imaging offers a significant advantage in guidance and monitoring of acoustic therapy, namely, imaging in real-time. Additionally, tissue characteristics such as ultrasound attenuation, elasticity, and temperature have been quantified using ultrasound imaging. Figure 2 shows an ultrasound-imaging-guided treatment of liver tissue.

The application of HIFU resulted in the production of a hyperechoic spot at the focus. The increased echo is thought to be due to bubble activity at the focus. This hyperechogenicity at the treatment site shows considerable promise for therapy targeting and monitoring.

**APPLICATIONS OF HIFU THERAPY**

The first clinical applications of HIFU were performed in patients with Parkinson’s Disease. HIFU was used to produce coagulative necrosis lesions in specific complexes of the brain. HIFU therapy currently is in clinical use to treat Benign Prostatic Hyperplasia (BPH) and prostate cancer. Clinical trials are also underway for treatment of fibroadenoma of breast, breast cancer, uterine fibroids, and a variety of stage 4 primary and metastatic cancer tumors of kidney, ovaries, and liver [1,2]. Also, significant advancements of image-guided HIFU therapy have been achieved by Chinese investigators in treatment of cancer. Proliferation and tumorigenesis after HIFU treatment has been observed to be significantly reduced with little or no toxicity, and adverse side effects. In a number of studies, HIFU treatment has been administered extracorporeally, without sedation or anesthesia, with complete patient tolerance.

A relatively new application of HIFU is hemostasis (arrest of hemorrhage) in trauma or elective surgery [3]. It has been shown that HIFU can effectively stop active bleeding from injured solid organs (liver and spleen), and major blood vessels. The acoustic hemostasis was long-lasting, and with minimal adverse effects.

Acoustic therapy appears to provide a promising, valuable tool for non-invasive therapy in medicine.

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Focused Ultrasound Surgery – Biological and Physiological Effects

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The main aim of using high intensity focused ultrasound beams for localised tissue destruction is to obtain instantaneous cellular damage within the target volume, while sparing overlying tissue structures. The mechanism by which focused ultrasound surgery (FUS) (also known as high intensity focused ultrasound (HIFU)) induces tissue ablation is primarily thermal in origin. Temperatures in excess of 56°C are maintained for times of 1 second or longer. This results in coagulation necrosis in the centre of the focal volume and a gradation of damage towards the edge. The occurrence of acoustic cavitation results in a different appearance of cellular damage, with “tears” appearing in the treated tissue. Review of the literature shows that the majority of histological study has been carried out in the brain, but more recently, hepatic lesions have been studied using both light microscopy and histochemical techniques.

**BIOLOGICAL EFFECTS**

The primary aim of a high intensity focused ultrasound exposure is to obtain rapid thermally induced coagulative necrosis within a well circumscribed target volume, while sparing tissue elsewhere. The most striking feature of focused ultrasound damage is the very sharp demarcation between viable and non-viable cells at the lesion boundary. It is generally accepted that temperatures in excess of 56°C held for 1 second or longer lead to instantaneous cell death [1]. It has been shown that if sufficient energy is applied very rapidly, then the final temperature achieved is independent of vascular perfusion and other cooling mechanisms [1-3].

The conventional description of a histological section of a thermally induced lesion is that of an “island” and “moat” structure [4,5,6]. Figure 1 shows this configuration in a dog prostate. In the brain, the “island” is a coagulated, densely packed core, and the moat shows liquefaction of nerve cells [5]. An alternative description used by a number of authors studying brain lesions uses concentric zones [7,8]. Åstrom *et al* [7] define zone I as the coagulated core. Zone II lies peripheral to this with zone III at its external boundary. Zone IV lies outside zone III and demonstrates reactive and reparative processes some time after lesion creation. An hour after focused ultrasound exposure, zone II is clearly seen using trypan blue uptake, zone I sometimes takes up this stain, but zone III does not. The tissue in zone II is loosely organised, and degenerative changes of cells are more marked in this zone than in zone I. 

Vykhodtseva *et al* [8] describe 5 types of damage in zone I, ranging from “light” to “severe”. The lightest damage consisted of liquefaction necrosis with pyknotic glial cell nuclei and pale, fragmented myelinated fibres. The most severe damage was in cores which were firm, showing coagulated necrosis and “dust-like” myelin. Electron microscopy of lesioned brain tissue reveals that synapses and mitochondria are amongst the first structures to be damaged [9,10]. The “island and moat” structure has also been seen in the prostate and in the liver [11-13]. 2 hours after lesion formation in the liver there is a rim of glycogen free cells at its boundary that appear otherwise histologically normal (zone IV). This rim is about 10 cells wide, and the cells are found to be dead 48 hours later [12]. Van Leenders *et al* [14] used immunohistochemical methods to demonstrate that
renal cells that looked normal using light microscopy, but that did not express the cytoskeletal protein CK8, revealed necrosis with cells lacking extra-cellular and nuclear membranes when studied using electron microscopy.

If the ultrasonic exposure conditions used are significantly above those to give purely thermal damage, light microscopy shows “holes” and “tears” in tissue that are characteristic of tissue water boiling, or acoustic cavitation.

EFFECTS ON BLOOD VESSELS

Åstrom et al [7] reported that the blood vessels in zones I and II of the grey matter were mostly unbroken, but appeared dilated and congested with erythrocytes which they thought had probably coagulated. Outside these zones, blood vessels were unaffected. Vykhodtseva et al [8] attempted to correlate tissue temperature as measured by magnetic resonance methods with the severity of damage observed. They concluded that at temperatures of 60-67°C destruction of blood vessels led to local haemorrhages, but that at temperatures above this no haemorrhage was seen presumably because all tissues were coagulated. Rivens [15] has shown that blood vessels of the liver may become obstructed as a result of focused ultrasound ablation, leading to death of tissues not directly targeted by the ultrasound beam (indirect damage). This is demonstrated in Figure 2. The ability of high intensity ultrasonic beams to occlude blood vessels in this way is being investigated as a possible adjuvant method for tumour therapy, and as a possible tool in fetal medicine.

FIGURE 2. Focused ultrasound array in rat liver. A region of direct ultrasonic damage is seen next to a region of indirect damage caused by the blockage of a feeder blood vessel.

SUMMARY

High intensity focused ultrasound beams are capable of inducing highly localised regions of coagulative necrosis and cell death at depth within tissue. No adverse effects are found in overlying or surrounding tissues.

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Ultrasound Guided and Monitored Focused Ultrasound Surgery

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Focused ultrasound surgery (FUS) has the potential to destroy unwanted tissue with very high spatial specificity. In order that this may be used to full advantage clinically, it is important that accurate targeting and monitoring methods are used. A number of sophisticated imaging techniques are available, but this goal may be most simply achieved using diagnostic ultrasound. While basic B-mode methods have not proved useful for imaging purely thermal lesions, other techniques such as elastography, reflex transmission imaging and vibro-acoustography have been investigated. The relative merits of these methods will be compared.

REQUIREMENTS FOR IMAGING OF FOCUSED ULTRASOUND SURGERY

It has been demonstrated that the margin between dead cells and live cells in a focused ultrasound lesion is very narrow (about 6 cells wide) [1]. In order that this high spatial specificity can be used to full advantage, thus ensuring that focused ultrasound surgery (FUS) is a truly conformal therapy, there are a number of requirements for imaging techniques used to target and monitor treatments. An important aspect of this is that the spatial resolution available is adequate to allow good delineation of the margins of the target volume to be treated. Any method of monitoring tissue damage created by FUS must be capable of providing real time or pseudo-real time imaging response to the changes induced. Such changes may include a temperature rise, changes in acoustic attenuation properties, or alterations in tissue stiffness. Following completion of the treatment an overall view of the ablated volume is useful. Magnetic resonance imaging of temperature rise has been used to good advantage [2]. However, if ultrasonic imaging methods capable of providing accurate and rapid assessment of FUS induced tissue damage may be found, FUS equipment may become more compact and therefore accessible to more users.

ULTRASONIC IMAGING METHODS

B-mode imaging

There have been a number of reports that FUS induced lesions appear hyperechogenic on B-mode [3-7]. It seems probable that this increase in echogenicity is associated with the appearance of gas within the target volume, either from acoustic cavitation, or from tissue water boiling.[7]. It is possible to interleave the therapy and imaging signals in such a way that it is possible to visualize the FUS lesion as it is produced [6,7].

Yang et al [8] carefully controlled their exposure conditions to try to ensure that they avoided bubble production. They reported that under these exposure conditions, the lesions appeared hypoechoic.

ATTENUATION MAPPING

It has been shown that the attenuation coefficient of ultrasonically lesioned tissue may be twice that of undamaged tissue [9]. This feature is used to advantage in reflex transmission imaging (RTI)[10,11]. Probably the simplest way to measure acoustic attenuation is to use a transmission technique. However, this becomes difficult in vivo, especially in regions which contain gas or bone. Simple analysis of tissue backscattering are complicated in inhomogeneous tissues. RTI uses a strongly focused transducer to generate a short pulse. A gate is set behind the focus, and reflections from tissues within the gate are analysed. If gate lies within a homogeneous region, the signal received is dominated by the properties of the tissues in the focal zone. The attraction of this technique is that it may be possible to use the therapy source as the imaging transducer [11]. This technique has been shown to be capable of visualizing FUS lesions in tissues ex vivo.

ELASTOGRAPHY

Thermal damage to tissue may be expected to result in an alteration of its Young’s modulus. “Cooked” tissues are palpably harder than “uncooked”. Changes in tissue elastic properties have been investigated by a
number of people with the intention of using them to image FUS treatments [12,13]. In elastography tissue is deformed pseudostatically by a small amount. Radio-frequency signals are obtained before and after compression. Using the assumption that the speed of sound is constant, the displacement between consecutive pairs of pre- and post- deformation echo segments is calculated using a normalized cross-correlation function. From the displacements, local tissue strain can be calculated. Stiff regions of tissue exhibit low strain. It has been shown that this method is able to detect FUS lesions in tissue [12,13], but this is not yet an on-line, real-time technique.

A related technique is that of dynamic elastometry [14]. Here, a low frequency vibration is applied to the tissue, and the resulting velocity pattern is assessed using pulsed Doppler techniques. This method appears to give good results in excised tissues. Further developments are required to convert this into a real-time monitoring method for clinical treatments.

**OTHER METHODS**

A number of other ultrasonically based methods have been proposed for imaging thermally induced FUS lesions. These include the proposal to map temperature by measuring changes in the mean scatterer spacing or echo displacement [14].

**REFERENCES**

The Medical Applications of Focused Ultrasound Surgery (FUS): a Review of the Clinical Experience

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To most clinicians, ultrasound is a useful diagnostic tool. Few are aware of its therapeutic potential. The ability to destroy a selected volume of tissue at depth within the body whilst sparing overlying tissue, in a way that is non-invasive, would seem to be ideally suited to the treatment of a number of medical conditions. This is the principle underlying focused ultrasound surgery (FUS), also called high-intensity focused ultrasound (HIFU). In recent years there has been a surge of interest in the medical applications of FUS, and encouraging clinical results have been published. The variety of benign conditions in which FUS has been reported to have some therapeutic success include: Parkinson's disease, glaucoma and benign prostatic hyperplasia. It has been used as a tool in pain research, and its ability to cause vascular occlusion is under investigation. The most useful application of FUS is likely to be in oncology, where it has been used to treat localised prostate cancer. Ongoing clinical trials at the Royal Marsden Hospital, United Kingdom, using FUS to treat metastatic liver disease, will be discussed.

INTRODUCTION

Focused ultrasound surgery (FUS), also called high-intensity focused ultrasound (HIFU), is based on the principle of bringing a high-intensity ultrasound beam to a tight focus within tissue. Deposition of sound energy is maximal at the focus, where its attenuation by the tissue causes heating and a rise in temperature sufficient to cause cell death. The energy deposited by the beam outside the focus is too small to cause any damage in the overlying and adjacent tissues. Focusing of the ultrasound beam may be achieved by using a 'curved bowl' transducer or by placing a concave lens in front of a planar transducer.

The main clinical advantages of FUS as a technique are:

1) it can be used extra-corporeally and is thus entirely non-invasive (particularly important when considering cancer treatments where seeding of tumour cells along needle/instrumentation tracks may cause problems);
2) accuracy of tissue damage. Each lesion is well-circumscribed histologically with a narrow boundary between normal and damaged tissue. This is a particular advantage if treatment is required to areas lying close to structures which have an important functional rôle (e.g. in the brain, or in the eye);
3) reduced anaesthesia can be used. Avoidance of a general anaesthetic means that the associated risks (albeit small) are also avoided. Some clinical groups use spinal anaesthesia, or local anaesthesia and sedation while others use no anaesthesia or sedation at all.

There is a great deal of ongoing pre-clinical work investigating potential future applications of FUS (e.g. exploring the ability to cause vascular occlusion and haemostasis), but in this paper we review the published clinical data on FUS.

BENIGN CONDITIONS

Much of the early development of FUS took place in the field of neurology. Patients with Parkinson's disease have a 'classical' triad of symptoms: bradykinesia (slow movement), cogwheel rigidity and pill-rolling tremor. Using FUS, Fry and colleagues treated 18 patients with Parkinson's disease [1]. A reduction in contralateral tremor and rigidity was seen in 13 patients. Although small numbers were treated and in most cases the therapeutic effect was of short duration (weeks-months), these were clearly promising results. The introduction of levodopa as drug therapy, however, was probably responsible for the halt to further research with FUS in this area.

Glaucoma

Glaucoma is characterised by raised pressure within the eyeball (intra-ocular pressure, or IOP), which can cause pain, loss of peripheral vision and ultimately blindness. The basic pathological 'fault' is an imbalance between production of aqueous humour and its removal. Experiments on porcine eyes showed that FUS could produce thinning of scleral collagen [2]. It was felt that the creation of this new route for the outflow of aqueous humour from the anterior chamber to the subconjunctival tissue was likely to be the principal mechanism behind the lowering of intra-ocular pressure observed with FUS treatment. Following some encouraging results from earlier trials, a multi-centre study was instituted in the USA [3]. 1,117 treatments of 880 eyes were carried out in 20 centres on an out-patient basis. The mean IOP pref-FUS was 38.1mmHg. At six months, the number with
an IOP of 25mmHg or less was 54.5%, and at 12 months 41.9%. This provided good-quality evidence of the effectiveness of FUS in a specific clinical scenario: an encouraging outcome.

**Benign prostatic hyperplasia**

Although drug treatment is often initially successful at relieving the symptoms and slowing progression of benign prostatic hyperplasia (BPH), a significant proportion of patients will need to undergo surgery at some point to relieve urinary outflow obstruction. These patients are frequently poor candidates for general anaesthesia and with a morbidity rate from surgery of 15-20%, urologists have been keen to explore the possibility of using minimally invasive therapies.

A number of early studies showed promising results with improvements in symptoms and urinary flow rates while few side-effects were noted (transient urinary retention and haematospermia). One group, reporting on longer-term efficacy, noted that 35/80 patients had had to undergo trans-urethral resection of prostate (TURP) within 4 years of follow-up [4]. Another study comparing four less invasive treatments with TURP found that although FUS had the lowest failure rate of the less invasive treatments, it was also associated with the lowest reduction in symptom score and lowest improvement in urinary flow rate [5]. It seems more likely that future involvement of FUS in urology is going to be in treatment of localised prostate cancer (\textit{q.v.}).

**FUS IN ONCOLOGY**

The majority of cancer patients are elderly, often have a number of co-morbid conditions and frequently have to undergo a number of surgical procedures. The advantages of minimally invasive treatments in such a group of patients are self-evident.

**Localised prostate cancer**

More widespread use of PSA (prostate specific antigen) testing for screening has meant that a greater proportion of prostate cancers are detected at an earlier stage than previously. These are more likely to be localised to the prostate. The morbidity from radical prostatectomy and radical radiotherapy has encouraged a search for less-invasive local treatments, including FUS.

The latest update to trials undertaken by Gelet and colleagues was published in 2000 [6]. 64/82 patients had been treated in either one or two sessions, and local control (negative biopsies and PSA less then 4ng/ml) could be achieved in 71/82 (87%). Overall 5-year progression-free survival was 62%.

Another group [7] treated only part of the prostate in the first 49 patients ('selective' treatment) while the whole prostate was treated in the next 62 patients ('global' treatment). Unsurprisingly, patients who had 'global' treatment showed better results.

Overall, the studies of FUS for localised prostate cancer show that it is effective and well tolerated. The lack of cumulative toxicity means that repeat treatments are possible and this is likely to be useful for patients who recur locally following external beam radiation. Indeed, this group of patients (and those who are unfit for, or unwilling to undergo conventional surgery) may be the source of recruitment to further phase II trials to see if additional refinements of treatment technique can be introduced to improve effectiveness and reduce complications still further.

**Malignant liver tumours**

There has been increasing interest in local treatments for both liver metastases and primary hepatocellular carcinoma. At the first International Workshop on the application of HIFU in Medicine held earlier this year in Chongqing, China, a number of Chinese groups presented encouraging results form their work using FUS in a variety of tumour types, including primary hepatocellular carcinoma. Data from ongoing trials using FUS to treat liver metastases at the Royal Marsden Hospital, United Kingdom, will be presented.

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A split focus can produce a broad heating pattern without forming unwanted secondary foci. The throughput of coagulation therapy with high-intensity focused ultrasound (HIFU) can be greatly improved by employing this method. Sonodynamic therapy was proposed based on the finding that certain chemicals are activated by acoustic cavitation and thereby induce a significant antitumor effect. Sonodynamically active cavitation can be efficiently induced through superimposing the second harmonic onto the fundamental. A focused ultrasound treatment system employing a split focus and second-harmonic superimposition for coagulation and sonodynamic therapy, respectively, is now being developed.

**SPLIT FOCUS FOR COAGULATION THERAPY**

The split-focus method was invented for creating a broad heating pattern without forming unwanted secondary foci either in front or behind the focal plane [1,2]. It can reduce the temporal and spatial peak acoustic intensity in ultrasonic hyperthermia by an order of magnitude in comparison with the conventional single-spot scanning approach. Recently, there have been several reports that it has potential usefulness also in coagulation therapy [3]. It can substantially improve the throughput of coagulation HIFU treatment through multiplying the volume of the focal zone. The ideal, theoretically simplest split focal field can be generated from a geometrically focused transducer with a circular aperture uniformly divided into many sectors. However, for an intracavitary transducer, a non-circular shape of aperture is needed to maintain its necessary area within the allowed width [4]. The width of each sector of a non-circular transducer must be optimized to produce a proper heating pattern.

**Prototype Split-Focus Transducer**

A prototype split-focus transducer with 8 sectors with an aperture of 40 mm X 20 mm was constructed for transrectal treatment of a prostate. The angles of the lines between adjacent sectors were determined based on the computer simulation of heating patterns. The PZT transducer has a resonant frequency of 3.2 MHz and a spherical curvature radius of 35 mm. It is contained in an aluminum housing in combination with a small imaging probe at 6.5 MHz (EUP-F331, Hitachi Medical) having a convex array curvature radius of 10 mm.

**Animal Experiment and Results**

Colon 26 carcinoma was subcutaneously implanted to male CDF1 mice. When the tumor size exceeded 15 mm in diameter, it was submerged in degassed water at room temperature and insonated with the prototype transducer. Insonation was continued for 5 s, and the ultrasonic intensity was adjusted so that boiling in tissue would start at 6 s. In Figure 1, cross-sections of the tumors insonated in the split focus mode and the single-spot focus mode are compared. A contiguous coagulation volume of more than 0.1 cm³, larger by an order of magnitude than the single-spot focus mode, was created with the split focus mode. It has been confirmed that significantly large lesion can be created even without tissue boiling if a split focus method is used with a transducer having properly designed sectors [5].

**FIGURE 1.** Murine tumor after coagulation treatment.

**SECOND-HARMONIC SUPERIMPOSITION FOR SONODYNAMIC THERAPY**

Ultrasonically induced cavitation may have potential therapeutic applications if it can be somehow
Recent in vitro and in vivo experiments have demonstrated that ultrasound can activate certain chemicals and thereby induce significant antitumor effects [6-8], which allowed us to propose a new modality of tumor treatment, "sonodynamic therapy". Acoustic cavitation is known to be induced by standing waves at much lower intensity than by progressive waves, but insonation with standing waves does not seem to be widely applicable to therapeutic treatments. We have found that sonochemically active acoustic cavitation can be efficiently induced even by progressive waves if the second harmonic is superimposed onto the fundamental [9-11].

**Focused Array Transducer for Second-Harmonic Superimposition**

In order to synthesize a focal field with second-harmonic superimposition, a focused array transducer with a co-focal alignment of its PZT elements at the fundamental (0.5 MHz) and those at the second harmonic (1 MHz) was devised. It was 100 mm in diameter and has a spherical radius of curvature of 108 mm.

**Animal Experiment and Results**

A xanthene derivative, erythrosine B was intravenously administered to the mouse at a dose of 50 mg/kg. After surgical anesthesia to a ddY mouse, a liver lobe was exteriorized. The mouse was held in degassed saline at 39°C and its position was adjusted to locate the lobe at the focal spot so that the focused ultrasound propagate perpendicularly through the lobe. The effect of second-harmonic superimposition with and without administration of erythrosine on producing focal tissue damage, typically 3-4 mm in diameter, paired with fractional harmonic emissions are shown in Figure 2. The results are plotted with the fundamental and the second-harmonic focal-spot average intensities on the horizontal and vertical axes, respectively. Each insonation was continued for a maximum of 3 min until tissue damage was observed. Synergism between the fundamental and the second harmonic in producing cavitation tissue damage is quite distinctive in the presence of erythrosine. Cavitation tissue damage was observed when focal-spot average acoustic intensities at both frequencies was 1 W/cm² or higher. This intensity thresholds is lower by orders of magnitude than those for conventional methods. Insonation with second-harmonic superimposition in combination with a certain sonodynamically active agent may have potential use for selective tumor treatment.

**ACKNOWLEDGMENTS**

A focused ultrasound treatment system employing a split focus and second-harmonic superimposition for coagulation and sonodynamic therapy, respectively, is now being developed under entrustment by the New Energy and Industrial Technology Development Organization of Japan.

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In vivo tests of a noninvasive large-scale phased array system for deep ultrasound surgery under MRI control


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A new integrated MRI compatible focused ultrasound system was tested in preparation for clinical trials. The system consists of a phased array transducer, a 4-axis positioning system, computer control, and a thermal dosimetry workstation. The phased array could control both the depth of the sonication and the volume of the focal area. It is integrated with the MRI unit. Individual sonications and volumes were thermally ablated with FUS in pig thigh muscle in vivo. The sonications were up to 10 cm deep.

INTRODUCTION

In this study the performance of an approximately 200-channel clinical ultrasound phased array system was tested during thermal surgery deep in tissue. The system was manufactured by TxSonics Inc. (Haifa, Israel) and was designed to use magnetic resonance imaging to aim and control the ultrasound exposures. The phased array system allowed electronic control of the depth of the focal spot and also the size of the coagulated volume. We tested the system by sonicating 10 pigs (approximately 40 kg) in vivo. The results showed that the system can reproducible coagulate tissues at depths up to 10 cm the maximum tissue depth available in the pigs. An integrated theoretical predictor for the ultrasound power gave good initial values for the lesion size. The transducer was able to tilt about its central axis. This allowed added flexibility in targeting locations behind bones. The system performed reliably. As a conclusion, these preclinical large animal tests demonstrated the feasibility of using this large-scale phased array system for deep thermal surgery.

MATERIALS AND METHODS

Sonifications were delivered 2.5-10cm deep into the thigh muscles of ten male pigs. The pigs’ skin was shaved before the procedure, and they were coupled to the FUS system with degassed water and ultrasound gel. A surface coil and later a pelvic coil (USA Instruments, Aurora, OH) was used for the imaging. The positioning system was built into a standard MRI table (Figure 1). A 1.5T clinical MRI unit was used (GE Medical Systems, Milwaukee Wisconsin). Individual sonications were delivered at varying powers and with different phasing patterns. Additionally, overlapping sonications were delivered in order to treat contiguous volumes at different depths.

During the sonications, a gradient echo sequence (TR/TE=39.9/19.7 ms, flip angle=30°, FOV=28 cm, matrix size=256x128, 0.75 NEX) was used to estimate the temperature changes during the sonications (1,2). The resulting tissue damage was evaluated in T2 and contrast enhanced T1-weighted fast spin echo imaging. The system was integrated with the MRI scanner; it prescribed the imaging sequences, triggered the scanner, and calculated the temperature maps. The thermal dose model (3,4) was used online to estimate the extent of the thermal tissue damage.

RESULTS

The system was capable of creating lesions at varying depths in pig thigh muscle. The size of the resulting lesions could be controlled by using different phasing patterns. Some example results are shown in figures 2 and 3.
Figure 2 shows examples of temperature maps for three sonications at 3, 5, and 8 cm deep in the tissue. The resulting lesion sizes for these sonications were approximately 20x12, 25x12, and 30x10 mm respectively for the 3, 5, and 8 cm deep sonications (measured in T2-weighted images). Two phasing patterns were used in the sonications shown in this example to increase the focal volume. In the 3 and 5 cm deep sonications, the focal volume was increased more than in the 8 cm deep sonication. The phasing also controlled the depth of the sonication.

Figure 3 shows T2 weighted images acquired after a volume was treated 8 cm deep in the tissue with 23 overlapping sonications. The dimensions of this treated tissue volume was approximately 40x30x30 mm. In contrast-enhanced images, the treated area was seen as a uniformly non-enhancing area surrounded by a hyperintense rim, indicating that the volume was thermally coagulated (5).

DISCUSSION

This MRI guided FUS surgery system is capable of thermally ablating large tissue volumes deep into tissue. The tests described in this study were designed to be a precursor to clinical tests with this system.

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Laparoscopically Delivered HIFU for Partial Renal Ablation

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Our purpose is to develop a high intensity focused ultrasound (HIFU) probe to ablate kidney laparoscopically. A Sonablate™ 200 HIFU system (Focus Surgery Inc., Indianapolis, IN) was used in acute (n=10) and chronic (n=5) experiments to ablate Yucatan mini-pigs’ kidneys. A 5 Fr ureteral catheter was inserted into the renal pelvis and 10 cc of air was instilled into the kidney. The HIFU probe was inserted through a 30-mm trocar placed at the level of the umbilicus. The targeted renal pole was treated aiming to ablate a 21´17´10 mm3 tissue volume. HIFU induced average lesion size of 23´17´11 mm3. 10 animals were sacrificed at 4 days and 5 animals at 15 days following surgery. Gross and microscopic examination revealed homogenous and complete tissue necrosis throughout the entire volume of the lesion with sharp demarcation from adjacent normal tissue.

We were able to refine a 15mm probe for laparoscopic HIFU delivery capable of simultaneous ultrasonic imaging. Partial renal ablation using this probe is feasible and safe, and results in homogenous, complete and reproducible lesions.

INTRODUCTION

There is an increasing interest in the laparoscopic techniques for performing nephrectomy. The uro-surgical community is currently investigating several laparoscopic techniques. Notable examples are: cryoablation, radio-frequency (RF) ablation, and high intensity focused ultrasound (HIFU) ablation (Gill et al., 2000). HIFU technology has demonstrated promising results in the treatment of benign prostatic hyperplasia and prostate cancer (Madersbacher et al., 1995; Sanghvi et al., 1999). A notable example of HIFU systems is the Sonablate™ device developed by Focus Surgery Inc., Indianapolis, IN (http://www.focus-surgery.com). The Sonablate™ makes use of a proprietary transrectal image-guided HIFU technology to treat prostate diseases by rapidly elevating tissue temperature about 90° C to produce coagulative necrosis. In this feasibility study, we extended the application of the Sonablate™ device for laparoscopic kidney tumor ablation.

I. MATERIAL AND METHODS

A. Sonablate™ Device

The Sonablate™ 200 HIFU device (Focus Surgery Inc., Indianapolis, IN) was used to image and localize kidney tissue for ablation, and to monitor and control the treatment parameters during the laparoscopic procedure. A complete description of the device has already been given in several publications (Sanghvi et al., 1999).

B. Laparoscopic HIFU Probe

The probe consists of two main parts: (1) probe assembly, and (2) supporting sleeve.

B.1. Probe Assembly

The laparoscopic probe assembly parts are shown in Figure 1. Two major modifications were implemented to standard Sonablate™ prostate treatment probe.

1) The probe tip was redesigned and built from Stainless Steel to adapt to laparoscopic surgery requirements.

2) A new piezoelectric transducer (4.0 MHz, 30-mm focal length, 12×30 mm aperture) was built with a geometry that was adaptable to the new tip.

B.2. Supporting Sleeve

The supporting sleeve (Fig. 1A) made from Stainless Steel has two functions: (1) protection of the latex sheath during the probe insertion, and (2) providing an acoustic window to allow the latex sheath to extend in the desired plane only. It covers the latex sheath while its opening is aligned with the window on the probe tip (Fig. 1B).

B.3. Transducer Calibration

The transducer was fully characterized by measuring its electrical impedance, acoustic field, and total acoustic power output. It was able to generate acoustic power levels up to 35 W that corresponded to focal intensities over 2200 W/cm2 in tissue that would be sufficient for tissue ablation through rapid temperature rise (>90° C) and possible vaporization.
C. Animal Model

Fifteen female Yucatan pigs, weights ranging from 40 to 55 kg, were used in this approved study. The lower pole of the right kidney was treated in all the pigs.

D. In Vivo Experimental Procedure

Fifteen pigs were divided into two groups. The first group (n=10) was used for a sub-acute, 4 days survival study and the second group (n=5) was used for a chronic, 15 days survival study. All pigs were treated under general anesthesia and standard sterile surgical procedure. A urethral catheter was inserted into the kidney to be ablated and 10 cc of air was instilled before starting HIFU treatment. The air bubbles acted as a shield to block the ultrasound beam from propagating to the far end of the kidney. Two laparoscopic trocars were inserted into the abdominal cavity. The probe tip was then advanced to the desired area of the lower pole of the right kidney. The kidney was imaged in the transverse and longitudinal planes. The treatment zone was selected on these images. The treatment was performed using 26 W of total acoustic output power and On/Off exposure cycles of 5/6 seconds.

At the end of the procedure, the abdominal openings were sutured and the animal was returned to the cage.

II. RESULTS

Immediately after the procedure a coagulated, blanched area appeared on the surface of the kidney. In both group of animals after sacrifice a well-defined necrotic lesion was found in the targeted region. The dimensions of the lesion were in good agreement with the desired dimensions set through the Sonablate<sup>TM</sup> treatment planning that was 22×17×11 mm ± 1 mm. Gross pathology (Figure 2) and histology showed well-delineated homogeneous lesions.

III. CONCLUSIONS

Contiguous necrotic lesions were created in the lower pole of the kidney extending from the pelvic system to the capsule. The appearance of a hyperechoic region observed in the ultrasound B-mode images around the focus supports that cavitation may also have a significant role in this mode of tissue ablation. It is anticipated that necrotic tissue volume will significantly reduce bleeding during partial nephrectomy.

ACKNOWLEDGEMENTS

This work was funded in part by the New Energy Development Organization (NEDO), MITI, Tokyo, Japan.

REFERENCES


This paper describes the use of the strongly focused ultrasound energy to perform non-invasive surgery on well-defined sub-cutaneous volumes, that is, High Intensity Focused Ultrasound Surgery. It briefly outlines the development from the early uses in experimental animals (1), to the present where sophisticated equipment is having clinical trials. The basic physics of heating small volumes will be reviewed, with discussion of the shapes of lesions that can be achieved. Physical and biological limits to the procedure will be suggested, as well as the critical role of lesion imaging. Notwithstanding the progress that has been made, HIFUS has not become a standard clinical tool as yet, although in some places it is very close to achieving this status. With much of the required technology in place, the future depends on identification of sites where HIFUS can be competitive with existing treatment modalities.

DEFINITION

“HIFUS” stands for High Intensity Focused Ultrasound Surgery. It covers the generation of powerful ultrasound beams through the use efficient, high power transducers, with some system of focusing, so that regions of high intensity, hence strong heating in tissue, can be used to ablate, that is, to destroy, small volumes of tissue.

ORIGINS

The understanding of acoustics goes back to the 19th century. (Rayleigh) The fact that an acoustic wave can transport energy and deposit it in an absorbing medium was also well understood. Bio-medical applications followed the demonstration of ultrasonic propagation, and the ability to make sources of considerable power, and to focus the beam.

Nyborg 1 has collected the recollections of many of the pioneers. Very early, and typical, was the work of Padmarkar Lele in creating lesions in cat brains in 1962. He established the use of a strongly focused beam that has been followed since. The earliest application that reached the stage of clinical use was the treatment of ocular tumours, by F.L. Lizzi and colleagues from the 1970's on. From there we can legitimately fast-forward to 1993. In that year European Urology published a supplemental issue on Thermal Tissue Ablation2. Several designs for ultrasound ablative surgery are presented there, mostly following the same basic principles.

BASICS

The essential features of a HIFUS system are shown in Figure 1. The energy source is the transducer, here depicted as having the shape of a spherical bowl. The resulting ultrasound beam comes to a focus at a distance F, producing, typically, a cigar shaped region of high intensity. For HIFUS applications, this volume is located below the skin surface, at the treatment depth, D. With ultrasound it is necessary to couple the transducer and skin using a water or acoustic gel path.

FIGURE 1 The essentials of a HIFUS system.

Tissue Properties

The frequency is governed by the attenuation/absorption properties of the tissues. For most tissues the attenuation, \( \mu (\text{dB/cm}) \) is given as a function of the frequency, \( f (\text{MHz}) \) by, approximately:

\[
\mu = b (f/f_0)^m
\]

(1)

Here \( b \) is the range from 0.1 (dB cm\(^{-1}\)) when \( f_0 \) is set to be 1 MHz. For a majority of soft tissues the attenuation is due to absorption, with the index \( m \) ranges from 1.0 to 1.4. This governs both the loss of energy as the u/s wave penetrates the tissue, and absorption at the focus. For heating at depths of from 1 to 6 or 8 cm, the frequency varies from about 10 to 1.5 MHz.\(^3\)

Focal Volume

The dimensions of the focal volume (Figure 1, FV) are found from the Huygens-Fresnel principle \(^4\). The sources used often have a large aperture, so the Fraunhofer approximation should be used with caution. Since the intensities are large, non-linear propagation can be important in tissues near the focus \(^5\). Figure 2 presents field calculations for a typical system.
FIGURE 2 Acoustic field of 8.4cm dia, 15cm focal length, 1.7MHz source. Z – beam direction; R – radial direction. Dimensions in cm.

Operating parameters

Table 1 Typical operating parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>1.0 - 10 MHz</td>
</tr>
<tr>
<td>Focal length</td>
<td>3 - 15 cm</td>
</tr>
<tr>
<td>Peak intensity</td>
<td>200 - 1200 W cm^-2</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>1 - 5 seconds</td>
</tr>
<tr>
<td>FV diameter/length</td>
<td>0.2 - 2 cm</td>
</tr>
</tbody>
</table>

Lesion formation and characteristics

HIFUS systems as specified above can heat tissues to the temperature of protein coagulation, 55°C to 75°C, within a few seconds. The lesions comprise a central region of coagulation or cell destruction surrounded by a narrow boundary zone. Their shape conforms fairly well to the F.V. Lesions can be placed in closely packed arrays to give larger treated volumes.

Precautions

With excessive intensity, voids generated by cavitation or boiling will scatter and absorb power from the beam, and distort the lesion shape. Coagulation can enhance absorption, leading to further undesired heating. These effects are particularly disruptive to the formation of closely packed arrays. They also contribute to the displacement of the centre of coagulation toward the source side of the FV. Most important, the secondary intensity maxima on the source side of the focus (Figure 2) can lead to significant heating and damage to sensitive tissue in that region. This is notable when lesions are made near the skin, which has a much higher absorption coefficient than subcutaneous tissue. It may also be important in the transrectal treatment of the prostate, where the rectal wall must be spared.

Imaging

Lesions can be positioned, subcutaneously, with a precision of the order of one mm. Targets must be identified and tracked with similar accuracy during the treatment. Many lesions do not show on ultrasound imaging for up to hours after the treatment. A promising modality is MRI, using temperature measurement before and during treatment. Combining MRI with HIFUS is a complex problem, but it does not appear insoluble, and progress is being made.

PRESENT STATUS

At present HIFUS applications are constrained by having to avoid regions where gas or bone are present, where there is not too much breathing or cardiac induced motion, and where the sites are of moderate size, with well defined boundaries. In addition to the ocular work of Lizzi, treatment trials in CA liver, prostate and bladder have been or are being performed. Phase II trials of >66 patients at the ICR in London UK have shown that liver treatments can be carried out safely with little or no patient discomfort. Prostate trials of over 200 patients (CA and BPH) in 4 centres have given promising results but the modality has not reached full acceptance. No fundamental impediment has appeared, but lesion imaging and agreement on treatment end points are, finally, of great importance. The technology is either in place or in sight. When a clinical problem for which HIFUS becomes an accepted modality appears, it will prove its worth and develop to other applications.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge many years of collaboration with Drs C.R.Hill, G.R. ter Haar, and I.H.Rivens, at the ICR, and with Drs. G.Santyr and J.Wallace at Carleton University.

REFERENCES


b At the time of writing, the author did not have access to the results presented at the Workshop on the Application of High Intensity Focused Ultrasound in Medicine, Chongqing, China, May 10-12, 2001.
Ultrasonic intraductal devices for gastrointestinal therapeutic applications

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Many forms of cancer are difficult to treat because they are discovered at relatively advanced stage and because they do not respond very well to systemic forms of treatment like chemotherapy. This is the case for many cancers of the digestive tract. Ultrasound surgery, which is intense heating of malignant tissues by ultrasound absorption, has since proved effective in a wide variety of different applications. Most of these approaches involve external focused transducers. Unfortunately, many parts of the gastrointestinal tract cannot be treated in this way because of their inaccessibility. A solution is to position miniature ultrasound applicators interstitially and deliver energy locally. We developed two different applicators for the treatment of biliary and oesophageal tumours. The biliary applicator is a 2m long 3.6mm in diameter flexible catheter provided with a 8x2.8mm US transducer. It can be inserted over a guide-wire into a 4.2mm operating channel. The oesophageal applicator used the same architecture but the overall diameter is 10mm and it includes an ultrasonic mini-probe to image the treated zone. The two applicators allow sectored coagulation necrosis by rotating the flexible from outside. Animal trials were conducted with the oesophageal applicator and ten patients were treated using the biliary one.

INTRODUCTION

Although interstitial techniques are invasive, they are still the first-line option for treating certain types of tumour. They are mainly applied to tumours that are either inoperable or located so deep that access is complicated. Many different types of radiation have been investigated but ultrasound has been shown to be the most effective for treating deep lesions (Diederich, 1996). All the various applicators that have been developed are designed to achieve the same end: to increase temperature locally. For therapeutic purposes, such heat can be used in two different ways. In the first, usually referred to as hyperthermia, temperatures of up to 45°C are induced and maintained for long periods. This can be used in conjunction with radiotherapy. The second way involves generating much higher temperatures over a shorter exposure period (of the order of seconds) in order to induce coagulation necrosis (Fry, 1954). This method eliminates the problems associated with perfusion which means that heat redistribution around the target area can be more effectively controlled. This procedure involves using focused ultrasound transducers which can generate acoustic levels of the order of several hundred W/cm² at the focal point which is not possible with the small transducers which are suitable for interstitial applications. However, using interstitial technique, it is possible to induce coagulation necrosis of large volumes of tissue in a fairly short time (a few minutes) by using small, non-focused ultrasound transducers with a high emission frequency (Lafon, 1998). Using this technique two different applicators were designed one for the biliary duct cancer and the other one for the oesophagus cancer.

THE TWO APPLICATORS

Previous in vitro and in vivo experimental results demonstrate that interstitial ultrasound applicators with plane water-cooled transducers operate effectively to induce deeper coagulation necroses than other interstitial devices without thermal diffusion. The non-divergent shape of the active surface makes it possible to reach deep-seated volumes that are spared if a cylindrical transducer is used. If the transducer is rotated, sector-based lesions can be obtained with a short exposure time (<10 s).

The biliary applicator has been described in details elsewhere (Prat 1999). Briefly the active part embedded in the tip consists in a water-cooled piezoceramic plane transducer (3 x 10 mm²) operating at 10 MHz. The water-cooling enables to remove transducer self-heating. It also participates to ultrasound coupling between the transducer and the targeted tissues. An ultrasound transparent envelope is sealed over the applicator tip in order to ensure the watertightness of the cooling circuit. A 200 cm long flexible shaft for rotational motion control at distance is glued at the opposite extremity of the active part. The connecting end of the probe can be attached on a holder and rotated on its axis for as many times as desired. The rotation angle of the probe can be controlled by a micrometric screw. This probe is compatible with a 4.2 mm channel as commonly available on jumbo duodenoscopes. At least a micro-tube along the length of the 2 m long flexible shaft enables the path of a 0.021” guide-wire.

FIGURE 1. Schematic view of the oesophageal applicator
The oesophageal applicator used the same architecture but the overall diameter is 10 mm and it includes an ultrasonic mini probe to image the treated zone. As shown figure 1

RESULTS

Two different applicators were developed for the treatment of biliary and oesophageal tumours.

Biliary applicator

We demonstrate first the possibility of inducing in vitro and in vivo rapid coagulation necrosis of sizeable dimensions using an interstitial ultrasound applicator fitted with a plane transducer. The lesions depicted figure 2 was obtained on a pig liver. The sequence consisted of enchaining the 20 shots. There was a 5 s pause between shots so that the applicator could be rotated.

FIGURE 2. Treated volume after 20 shots

The anti-tumour effect of high intensity ultrasound has been studied and proven in various models, mostly with focused ultrasound (HIFU). It remained to be confirmed with this type of non-focused high intensity ultrasound. Our rate of 64% tumour-free animals after treatment is a satisfactory result, in a tumour model which is particularly aggressive, with almost 100% recurrence rate after surgical resection. Encouraging animal experiments prompted us to start a pilot clinical trial to determine the feasibility and short-term efficacy of this new therapeutic method on biliary tumours. Up to date 10 patients were treated and the clinical results will be published in few days. Without discussing these results here we may affirm that these clinical results are very encouraging.

Oesophageal applicator

Only animal trials were conducted using the oesophageal plane rotating transducer in order to determine the maximum thermal dose applicable on an healthy oesophagus. Results obtained on oesophagus pigs show that it was possible to induce homogeneous sector based or cylindrical coagulation necrosis without risk of perforation. Figure 3 (left) shows the mucosa start of scar after 25 shots of 14 W/cm² and 10s of duration with an angular step of 18°. In contrary, figure 3 (right), using the same angular step but a 15s shot duration macroscopic examination showed local perforations which could lead a negative vital prognostic for the patient. Following all the experiments the ethical comity has given its agreement for a pilot clinical trial.

CONCLUSION

These studies were conducted to prove the efficacy of an interstitial or intra-ductal applicator with a plane transducer to induce rapid necroses on large volumes. The applicator was rotated on its axis to produce cylindrical or sector based lesions. Each elementary lesion was obtained in maximum10 seconds and thus may be considered as non perfusion dependant allowing a precise definition of its geometrical location. The anti-tumour effect of high intensity ultrasound has been studied and proven in various models, mostly with focused ultrasound (HIFU). It was confirmed with this type of non-focused high intensity ultrasound. A high-intensity ultrasound probe for “through the scope” intra-ductal tumour destruction was developed and the clinical results on bile duct carcinoma are particularly encouraging. An oesophageal probe was also designed and the first clinical trials would be begin soon. Different versions of applicators can be developed for the percutaneous-transhepatic route, as well as for other applications in the digestive tract.

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Theoretical predictions and experimental results for non-invasive disease treatment via High Intensity Focused Ultrasound: a comparative study

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High-intensity focused ultrasound (HIFU) is becoming a widely accepted and “clean” modality to induce noninvasive coagulative necrosis of biological tissue for both cancer treatment and hemostasis. In this work, simulated results of HIFU treatment in turkey breast are analyzed and compared with equivalent in vitro experimental results. Attention is mainly focused on temperature and lesion evolutions; in particular, induced lesion boundaries and collateral damage to surrounding areas. The theoretical model (MEDUSA, MEDical UltraSound Algorithm), based on coupled acoustic full-wave solution and bioheat transfer equation, accounts for nonlinear sound propagation in inhomogeneous media, arbitrary frequency power law for acoustic attenuation, and temperature and lesion time histories. Our results show good agreement between the simulated lesions and the lesions created in fresh turkey breast in vitro.

THEORETICAL BASIS

The propagation of acoustic waves in a fluid is governed by Euler's equations, which express the conservation of mass (continuity equation) and the transfer of momentum (momentum equation) in a fluid volume, together with a thermodynamic equation of state. Acoustic nonlinearities are introduced by retaining the first two terms of a Taylor series expansion of the equation of state, yielding the well accepted B/A nonlinear model. To account for attenuation and dispersion through independent relaxation processes, the continuity equations is modified by the introduction of the time convolution operator $\ast$ following the approach of Szabo [1]. Equation (1) shows the complete system of governing equations for nonlinear acoustic propagation in lossy media in terms of acoustic pressure and velocity.

\[
\kappa \frac{\partial p'}{\partial t} = -\nabla \cdot \mathbf{v}' - \nabla \rho_0 - 2 \left(1 + \frac{B}{2A}\right) \kappa \ast p' \nabla \cdot \mathbf{v}'
\]

\[
\kappa = \kappa_\infty \delta(t) + \sum_{i=1}^{\infty} \kappa_i \frac{e^{-t/\tau_i}}{\tau_i} u(t)
\]

Values for the bulk moduli $\kappa_\infty$, $\kappa_i$, and relaxation times $\tau_i$ are obtained by a nonlinear least square fit procedure to the frequency dependent attenuation and phase speed expressions derived by Nachman et al. [2] to match the correct frequency power law in biological media.

During acoustic propagation in lossy media energy is transferred from the propagating wave to the absorbing medium and it is transformed into heat. Hence a distributed thermal source appears over the domain covered by the sound field whose density per unit volume is equal to $Q = -\nabla \cdot \mathbf{I}$ where $\mathbf{I} = \langle p' \mathbf{v}' \rangle$ is the acoustic time average intensity. This thermal source is responsible for the temperature increase in the medium and is the coupling term between sound propagation and temperature dynamics governed by the bioheat transfer equation.

\[
\rho C \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) - wC(T - T_0) - \rho C (\mathbf{u} \cdot \nabla T) + Q
\]

The first term on the right hand side of (2) describes heat conduction, the second term accounts for perfusion losses, and the third term models advection processes when blood flow in larger vessels is present.

Numerically we solve the system of equations for acoustic propagation by a pseudospectral time domain (PSTD) method. The PSTD method is based on the use of discrete Fourier transforms to evaluate the spatial derivatives of a function and it yields high order of approximation limited by the Nyquist theorem. Integration in time is performed by a staggered fourth-order Adam-Bashforth (AB) routine where pressure values exist on integer time steps and velocity values are interlaced at half time steps. Due to the periodic nature of Fourier Transforms, perfectly matched layers absorbing boundary conditions are included in the
acoustic propagation subroutine by the introduction of complex coordinate stretching [3]. Solution of the bioheat transfer equation is obtained by standard fourth-order finite difference techniques for spatial derivatives while integration in time is achieved by a third-order (AB) procedure.

EXPERIMENTAL PROTOCOL

A sample of fresh, turkey breast is placed in a sample holder (5x5x7cm) and immersed in a water tank maintained at a constant temperature of 37 °C. The treatment transducer (3.5 MHz, 23 mm diameter, 35 mm focus, 40 W input power) is placed in contact with the tissue such that the focal area coincides with the center of the sample holder. Before treatment is commenced, values of acoustic velocity and attenuation are obtained for the specific tissue sample from time of flight and amplitude data. These values are used as input parameters to the numerical algorithm. HIFU treatment is applied in CW for either 5s or 10s. After treatment the tissue is sliced, digital pictures of each slice are stored, and the lesion’s dimensions recorded. Image processing and edge detection is performed on each image and the lesion reconstructed in three dimensions. The reconstructed lesions are then compared with the lesions generated by the computer model for agreement.

RESULTS

Theoretically predicted lesions by the simulation algorithm agree well with the experimentally obtained lesions in turkey breast. Figure 1 shows a typical results for 5 seconds ultrasound exposure (left) and 10 seconds exposure (right). The 3D reconstructed experimental lesions are compared with the corresponding 3D lesions predicted by the model indicating a good fit in shape as well as volumetric prediction. A comparative statistical analysis at the 95% confidence interval is reported in Table 1. As illustrated, the 5s numerical results fall well inside the 95% confidence interval of the experimental lesions obtained at the same exposure time. A small discrepancy is found on the 10 seconds exposure which might be due to the small number of sample lesions.

FIGURE 1. Comparison of 3D reconstructed experimental and numerical lesions at 5s exposure (left) and 10s exposure (right).

<table>
<thead>
<tr>
<th>Lesion after 5 sec exposure</th>
<th>Lesion after 10 sec exposure</th>
</tr>
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<tbody>
<tr>
<td>Experiments</td>
<td>Experiments</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>Width (mm)</td>
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<td>12</td>
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<td>13</td>
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</tr>
<tr>
<td>13</td>
<td>1.7</td>
</tr>
<tr>
<td>11</td>
<td>1.8</td>
</tr>
</tbody>
</table>

95% Confidence Interval  
Lesion after 5 sec exposure | Numerical | Numerical | 95% Confidence Interval  
Length (mm) | Width (mm) | Length (mm) | Width (mm) |
| 10.58-12.25 | 1.55-1.83 | 15.7-18.3 | 1.85-2.54 |
| 10.58-12.25 | 1.55-1.83 | 15.7-18.3 | 1.85-2.54 |

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REFERENCES


The Role of Ultrasound in the Dolphin-Human Interaction

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The present work focuses on the acoustic characteristics of dolphin signals and on the possible effects they could have on the human biological system. One community of captive dolphins, three healthy volunteers and one person suffering from autism are the subjects of this study. The intensity, frequency and bandwidth of the signals emitted by dolphins towards each human-target are analysed and compared with the recordings of the signals used by the same dolphins in front of inanimate targets. The possible biological effects and psychological changes on the person suffering from autism are investigated. This study is preliminary to a research program on the Dolphin Assisted Therapy that is to date submitted to referee.

A PECULIAR KIND OF PET THERAPY

In recent years, the possible beneficial effect of dolphins on human beings in a therapeutic role has begun to draw the deserved attention. These marine mammals seem to be able to help improve the quality of life for people in all age groups and with hundreds of different disabilities [1]. This particular dolphin-human interaction has been called “Dolphin-Assisted Therapy” and falls within the ambit of pet therapy. Although the presence of water and the swimming with these marine mammals play an important role during the interaction, the crucial effect is due to the ultrasonic emissions that they use to scan the human body. However, the relationship between ultrasounds emitted by dolphins echolocating a person and the psycho-physiological state of the person, as well as the effects of ultrasounds on his state are not clear [2].

Acoustical characteristics of dolphin clicks

A small community of six bottlenose dolphins (\textit{Tursiops truncatus}) was placed in front of different targets, from inanimate objects of various materials to human beings: three healthy people and one suffering from autism. During each task the ultrasonic emissions (clicks) of these marine mammals were recorded and then processed using the mathematical functions within the MATLAB software libraries. Figures 1 and 2 show clicks’ profiles and the correlated spectra observed during experimental tasks. (All the data averaged on the total number of clicks). Comparison between the pulse in Figure 1, recorded during the interaction with the autistic person, and those in Figure 2, recorded during the tasks involving inanimate targets and

\textbf{FIGURE 1.} Sonar pulse’s profile and spectrum during the task with the autistic person.

\textbf{FIGURE 2.} Sonar pulse’s profiles and spectra during the tasks with, from above to bottom, plexiglas sphere, copper sphere, healthy human being with hydrophone on the head and healthy human being with hydrophone on the leg.
healthy people, points out how the acoustical behaviour of the dolphins is, in some cases very similar (in front of plexiglas sphere and human head) and in other cases very dissimilar (in front of copper sphere and human leg) to that taken in front of diseased person. It is possible to further investigate the problem by examining the frequencies versus the duration of the clicks. Figure 3 shows the overlapping between the acoustical windows used by the dolphins during echolocation of the different targets.

The acoustical window is the product of the sonar pulse pass bandwidth and its duration. The wider the window, the greater is the amount of information carried by the echo to the dolphin. These results suggest that dolphins modify the acoustical parameters of their sonar pulses not only in relation to the presence of an inanimate object or a human being able to produce some kind of interaction, but also according to the different part of the body investigated. In fact, during the interaction with a diseased person and a “human head” the animals tend to use a large pass bandwidth (45.4 kHz and 40.8 kHz respectively) shifted onto the high frequencies. This acoustic behaviour allows the dolphin to obtain detailed information about a specific part of the body and its biological inner structures using high frequencies. On the other hand, the use of a wide bandwidth enables some frequencies to cross a possible barrier, like a human skull, and interact directly with inner organs, possibly sending “messages” to the brain. The information contained in several clicks is equivalent to that contained in a “visual image”.

**Intensity of Clicks: Values Used in Medicine**

Another important characteristic of the clicks is their intensity, which assumes an intermediate value between those applied in diagnostic (80 mW/cm²) and in therapeutic medicine (2-5 W/cm²) [2]. As shown in Figure 4, the mean intensity used by dolphins to explore the human being is about 8000 W/m² and over 90% of it is within the 50-150 kHz frequency range.

These echolocation signals have all the physical characteristics to cause the biological, physiological and neuropsychological effects on human beings measured by some researchers. The high frequencies and peculiar intensity values that go with the wavelike motion of these ultrasound pulses could force a vibrational state, in a body subsystem, able to resonate with the affecting wave. These vibrational effects may be detected by the body as micro shocks that activated a defence mechanism inducing the hypophysis to increase the production of specific hormones such as endorphins and ACTH hormone. The action of the latter two can be manifold: to soothe pain, to raise response stimuli and, above all, to change the electrical activity of the brain [3], increasing slow alpha waves and hemisphere synchronization.

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Monitoring of Therapeutic Ultrasound Using an Acoustic Camera

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The feasibility of using an acoustic camera as a thermal imaging device for focused ultrasound surgery is investigated. The present study compares thermocouple measurements with time-sequenced acoustic camera images of tissue samples after applying high intensity focused ultrasound. Images are acquired using the Acoustocam (Imperium, Inc, Maryland) acoustic camera system. This apparatus replaces the lens, aperture, and sensors of an optical CCD camera with acoustic counterparts. The camera's image plane consists of a PVDF (polyvinylidene difluoride) piezoelectric divided into 128 X 128 pixel elements. The setup is operated in transmission mode, with a tissue sample placed between the camera and a 10 MHz illuminating transducer. Sections of fresh porcine liver and thigh muscle are placed in a bag containing degassed 0.9% saline and imaged. A high intensity CW ultrasound signal is then focused inside the tissue using a 2 MHz transducer. Images before, during, and after this sonication are examined. Time-dependent variations in image intensities are observed near the high-intensity focus. Additionally, permanent images are produced if the tissue is coagulated. Preliminary results indicate the camera may have application in guidance for ultrasound surgery in soft tissue such as the breast, where transmission can be applied.

INTRODUCTION

Transmission acoustic imaging situates an object between a source and receiver to provide a linear projection of its attenuation properties. The principle has been applied to develop orthographic images[1-3] to produce two-dimensional image reconstructions. A number of studies have revealed the potential of transmission techniques in medical imaging for recording the attenuation properties of varying tissues.[3-6] The present study examines the possibility of using transmission imaging to guide thermal therapies. We hypothesize that imaging thermally coagulated tissue with transmission ultrasound can achieve a higher signal to noise ratio than backscattered ultrasound, due to a strong change in attenuation coefficient and relatively low reflection coefficient. We also search for localized change in image intensity due to speed of sound variation caused by temperature changes, thus allowing the ultrasound focal region to be identified. Specifically, we test the transmission method with the acoustic camera system (i) for its ability to image coagulated tissue, (ii) the ability to identify the focus of a therapeutic ultrasound field in ex vivo tissue samples during sonication, and (iii) for correlation between image intensity and tissue temperature.

METHODS

The system uses a planar radiator, separated by a distance of 26 cm from the camera, to illuminate a large region of the target tissue. Ultrasound is focused onto the camera image plane using a compound system of acoustic lenses. The camera’s image plane consists of a PVDF (polyvinylidene difluoride) piezoelectric material divided into 128 X 128 active pixel elements deposited upon a standard silicon readout CCD multiplexer. The PVDF array is sensitive over a bandwidth of more than 20 MHz. Use of the standardized chip allows interfacing with commercial video and data acquisition equipment. The object plane is chosen using the zoom and focus on the camera, which is adjusted similar to an optical camera. Feedback is provided from real-time video images.

Tissue samples are placed in the camera’s image plane, as shown in Figure 1 and a focused transducer is placed perpendicular to the camera’s axis with its focus within the camera’s field of view. In separate experiments, an air-backed 1.1 MHz, 10-cm-diameter PZT transducer and a Tungsten-backed 1.8-cm-diameter transducer are used. Two types of sonications are performed, representing induced tissue temperatures below and above the coagulation point.

![Temperature Vs. Image Intensity](image.png)

**FIGURE 1.** Sonication in rabbit liver
Short, low power sonications are administered to test the capability to detect the focus at temperatures too low to cause physiological changes to the tissues. Higher temperatures, achieved using higher input powers and longer sonication times, were used to image coagulated tissue.

**RESULTS**

When sonications were performed at low powers, reversible image intensity changes were observed. Correlation of the image intensity with thermocouple measurements is illustrated in Figure 1 for the case of rabbit liver. Lesions were created in fresh porcine and rabbit muscle, as well as bovine fat. Images before and after high power sonication in porcine liver are shown in Figure 2. Lesion dimensions were measured on the resulting camera images and compared with sectioned tissue as summarized in the plot given in Figure 1. The image measurements (N=14) display good linear correlation with the actual lesion size.

**DISCUSSION**

When a high intensity CW ultrasound signal is focused inside the sample tissue a reversible, time-dependent variation in image intensity is observed in the region of sonication. This intensity changes appears to result from a phase variation caused by temperature change, resulting in a phase-contrast image. When intensities high enough to coagulate tissue are reached, the camera is able to image the lesioned area. Here, a relatively large change in the tissue absorption is the mechanism for the intensity change. Further investigation needs to be performed to fully assess the contributions of inhomogeneities away from the target area to the overall image intensity. The camera could potentially be modified from a broadband, pulsed signal to a continuous, single-frequency wave. This ability to select the source the frequency would provide more control over the beam attenuation and its sensitivity.

**FIGURE 2.** Plane in porcine liver, (a) before and (b) after high-intensity sonication. Lesion is located in upper center, as seen on photographed section (c).

**FIGURE 3.** Size of ultrasound induced tissue lesions

small structure. A higher frequency could be used in relatively homogeneous tissue to image smaller structures, where low frequency could be used to penetrate through thicker tissue regions to image larger structures, such as coagulated tissue. These preliminary results indicate the camera may have application in guidance for ultrasound surgery in soft tissue such as the breast and prostate where transmission can be applied.


An Acoustic Thermometer for Hyperthermia and Focused Surgery

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Given the high variability of tissue effects during sonication, temperature monitoring is one of the most crucial components for accurate thermal treatment of tissues with Focused Ultrasound (FUS) and other thermotherapy devices. Recently, the method of Ultrasound-Stimulated Acoustic Emission (USAE) has been introduced as a potential method for tissue measurements of mechanical properties of tissues. In this paper, the dependence of USAE on tissue temperature is determined. Since USAE depends on the acoustic and mechanical properties, which both vary with temperature, it is hypothesized that the USAE signal is also temperature-dependent and in such a way that it can be used to guide thermal therapy. Fresh porcine fat and muscle samples are exposed to ultrasound at power levels that induce temperature elevation. In both cases, the signal amplitude was found to follow temperature changes. These results indicate that USAE may have important promise as a potential method for thermal surgery monitoring.

INTRODUCTION

The temperature elevation in living tissues induced by any of the minimally invasive thermal therapies such as interstitial RF, microwave, ultrasound and laser probes depends on the local physical properties of the tissue that determine the amount of energy absorption and the local heat transfer induced by thermal conduction and blood perfusion [1]. These properties can vary significantly between different tissues and even between locations in the same tissue. Therefore, a given power of any of the thermal surgery devices can yield variable volumes of treated tissue and thus inconsistent clinical results. In order to overcome this uncertainty, the temperature elevation has to be locally monitored and controlled during treatment. Several imaging methods have shown promise in the monitoring and control of thermal therapies, with diagnostic ultrasound and MRI demonstrating the most potential [2]. In this paper, we demonstrate the dependence of the USAE (Ultrasound-Stimulated Acoustic Emission) [3] amplitude on temperature, whether and how it can be used for temperature detection and monitoring. The method is tested on a gel phantom and ex vivo porcine fat tissue.

METHODS

Two ultrasound beams with two slightly different frequencies were generated by two transducer elements. A single circular PZT-4 polycrystal with a diameter of 100 mm and focal distance of 80 mm was divided into these two elements by cutting the bowl in half such that the areas of both elements were the same. The driving radio-frequency (RF) signals were obtained from two function generators (DS 345; Stanford Research Systems, Sunnyvale, CA) controlled by a personal computer (PC) via an IEEE-488 communication line. Two RF-amplifiers were used (models 3100L and A150; Electronic Navigation Industry, Rochester, NY) to drive each piezoelectric crystal element. The ex vivo porcine muscle and fat tissue samples (all measurements were done less than 10 hours post mortem) were firmly attached in a holder that was positioned perpendicular to and in the focal zone of the beam in a water tank. A bare junction twisted pair copper-constantan thermocouple (Wire diameter: 50µm) was placed inside the tissue for the temperature measurements. The low frequency (19 to 21 kHz) USAE signal was detected at a location close to the thermocouple by a hydrophone (AQ-18; Benthos Inc., North Falmouth, MA) that was positioned in the water tank between the transducer and the sample. The signal received was registered with a digital oscilloscope (model 2431 L; Tektronix, Wilsonville, OR). The acoustical powers used were 6.6 W (100s (fat), 200s (muscle) CW heating/50ms PW cooling), and 10.6 W (60s CW heating/50ms PW cooling) and 17.2 W (200s CW heating/50ms PW cooling) for fat and muscle, respectively. At the beginning of each scan, 20 s of control data were acquired and at the end of heating, cooling followed.

RESULTS AND DISCUSSION

Figs. 1 and 2 summarize the results obtained from the muscle and fat samples, respectively. At low
power (within the hyperthermia temperature range), the USAE response (Fig. 1a) followed the temperature change detected at the thermocouple (Fig. 1b), i.e., during heating the amplitude consistently increased with temperature while during cooling it consistently decreased. At high power, the USAE amplitude variation rises during heating but starts decreasing before heating ends. This is due to the changes in the mechanical and acoustic properties of the tissue [4]. In the fat example (Fig. 2), the USAE amplitude variation is also shown to be highly correlated with temperature changes at temperatures both below and beyond the coagulation threshold (typically around 55°C) used for focused surgery. Figure 2(c) further demonstrates this point by showing high correlations during both heating (1.9% increase per °C, r²=0.968) and cooling (1.6% decrease per °C, r²=0.976). From Figs. 1 and 2 and a more extensive study [4], it can be concluded that at low power (before the onset of coagulation) the correlation between USAE and temperature changes is higher. At high power, the correlation is lost beyond a certain temperature, more so in the muscle than in the fat, due to irreversible tissue changes.

CONCLUSION
It was shown that the method of ultrasound-stimulated acoustic emission can be utilized in conjunction with focused ultrasound to yield a reliable method for detection and monitoring of temperature elevation. Porcine fat and muscle samples were used to demonstrate the high correlation between the USAE amplitude variation and temperature change during low and high power heating and cooling. With similar results obtained in liver [5], USAE was shown capable of detecting temperature changes as well as indicating the onset of coagulation in tissues [4].

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Treatment Planning for Transskull Ultrasound Surgery and Therapy

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Noninvasive treatment of brain disorders using focused ultrasound requires an accurate method for correcting ultrasound distortion. Previous studies indicate that control of ultrasound phase alone is sufficient for producing a focus in a known position through the skull. The present study concentrates on identifying practical methods that could be applied in a clinical setting. Ten ex vivo human calvaria are examined. Each sample is imaged in water using CT. The information is used to determine the inner and outer skull surfaces, the normal vectors along the surfaces, thickness as a function of position, and internal structure. Phase measurement over a series of points is obtained by placing a skull between a transducer and a receiver with the skull normal to the transducer. The data follows that predicted by a homogeneous skull model using a sound speed of 2650 m/s. However, large variance (S.D. = 1.05 rad) indicates the additional role of internal bone speed and density fluctuations. An algorithm is presented that corrects for phase aberrations and successfully produces a focus at a predetermined location through each of the skulls studied (N=10). Implementation of the method in a clinical setting discussed.

INTRODUCTION

Introduction

A series of studies have demonstrated that focusing of ultrasound through the human skull in predetermined locations is possible.\textsuperscript{1-3} Further, it has been shown that temperatures high enough to coagulate tissues can be achieved using this approach without producing excessive heating near the skull.\textsuperscript{4} The final step necessary for practical implementation of a transskull procedure is a minimally invasive or, ideally, noninvasive treatment plan. Other work has suggested a minimally invasive procedure using a catheter-inserted hydrophone is possible. The present study concentrates on recent work toward achieving a completely noninvasive method.

The central problem in developing a noninvasive approach lies in predicting the behavior of the ultrasound field after passing through the skull bone, which causes significant reflection, diffraction and absorption of the field. Successful prediction depends on developing correct and practical theory and methods. Practical considerations include obtaining accurate knowledge of the thickness and internal structure of the skull bone, precise registration between all points of the skull and the ultrasound array, and a computationally feasible model. Theoretical considerations involve finding a model as uncomplicated as possible without oversimplification of the problem.

Our approach is guided by initial experiments, which demonstrate that driving transducer elements in an array so that the acoustic pressure produced by each element arrives at the intended focal location in phase is sufficient for produces a sharp focus through the skull. Expectedly, it was found that skull thickness and density variations are major variables in determining this phase.

We have developed an algorithm to focus through the skull using thickness, density, and orientation obtained from CT images. The algorithm operates by projecting the field in the wavevector-frequency domain. Below, we outline the model and experimental procedure applied to ex vivo human skulls and discuss how this method could be applied in practice.

THEORY AND METHODS

The phase prediction algorithm for focusing through the skull operates in the wavevector frequency domain. The field from a small section of the transducer is propagated to the outer skull surface. At the outer surface the transmission coefficient is calculated as a function of incident angle before the transmitted (and refracted) field is propagated within the skull from the outer skull surface to the inner skull surface, and lastly from the inner skull surface into the brain tissue. The density within the skull is used to determine an effective skull sound speed for the relevant area. The present algorithm approximates a linear relation between density and effective sound speed.

Data for the simulation is obtained from a digitized human head profile obtained using CT images. Both the coordinates of the skull surfaces as well as the internal density variation are obtained from these images. The calculation is performed only in bone lying within the beamwidth of the section being considered.

Ten ex-vivo human calvaria are used in the study. Information about the shape and structure of an
individual calvarium is obtained by scanning the sample with a Siemens SOMATOM CT Scanner, returning images intensities proportional to material density. Scans were taken at 1 mm intervals using a 200 mm x 200 mm field of view. A polypropylene stereotaxic frame is attached around each sample to allow the skulls to be attached to the array and provide a reference for the mechanical positioning system and the CT images.

Coordinates of points along the inner and outer surfaces of the skull are identified on an image using a threshold filter, which searches for the innermost and outermost densities >1.4 gm/cm$^3$ along each line of an image. Points of successive images are combined to give three-dimensional representation of the inner and outer skull surface. Pixel intensities of each image are also combined into a three-dimensional array for later processing.

The phasing algorithm relies on precise knowledge of the orientation of the skull relative to individual array elements. To achieve this task in practice, the phasing algorithm translates and rotates the skull data from the CT coordinate frame to the Transducer coordinate frame as well as translate and rotate the skull from the mechanical positioning system's coordinate frame to the Transducer coordinate frame. The program operates using three markers $h_1$, $h_2$, and $h_3$ located at the intersection between reference bars on the polypropylene frame affixed to the skull. These locations may be identified mechanically with the positioning system to a precision of approximately 0.1 mm. However, in the CT images the 1 mm slice thickness limits the precision along the direction of the scan and makes the precise location of the marker difficult to accurately identify. Rather, an equation of the line is obtained by obtaining two position vectors $r_1$ and $r_2$ on each of the intersecting bars, so that the point of intersection between this bar and a second bar described by the primed vector $r'$ can be obtained by equating the two and solving for the point of intersection. The algorithm then generates a rotation matrix that maps between any of the coordinate systems.

$$R^T_n = \hat{A}^M R^M_n$$

where $\hat{A}^M$ is the rotation operator, $R^M_n$ represents $n^{th}$ coordinate in the mechanical positioning system frame.

**RESULTS AND DISCUSSION**

A driving phase pattern was generated for each skull in the study for a 320-element, 0.75 MHz transducer with a 15-cm radius of curvature. The array was operated using 10 W total power and field intensity about the target location past the skull was recorded using a scanned 0.2 mm hydrophone. In each of the skulls tested, a focus was produced in the target location after the phasing algorithm was applied. Figure 1 depicts a scan through a skull before and after the phasing application.

Overall results indicate that noninvasive correction for distortion due to transskull propagation is possible. Future investigation will concentrate on in vivo transskull focusing and high-intensity operation of the method. Combined with MRI for treatment monitoring this array could provide a completely noninvasive tool for the treatment of brain disorders.

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Ocular Drug Delivery using 20 kHz Ultrasound

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The cornea is a major pathway for drug delivery to diseased eye structures. However, the corneal epithelium is sealed with tight junctions, and often less than 1% of applied drugs can penetrate through. We have investigated the application of 20 kHz ultrasound, at an average intensity of 2 W/cm\textsuperscript{2}, for enhancement of corneal permeability to glaucoma drugs of different lipophilicity (carteolol, timolol, and betaxolol). The experiments were performed in rabbit cornea \textit{in vitro} using a diffusion cell. At an ultrasound exposure duration of 56 min, the permeability increased by 2.5 times for carteolol, 1.8 for timolol and 4.8 for betaxolol (p-value < 0.05). The permeability increase was usually accompanied by epithelial disorganization. Occasionally, structural changes in the corneal stroma were observed. The enhancement of permeability appeared to be a function of ultrasound exposure duration. The ultrasound and drug were also applied separately in order to distinguish immediate from long-term ultrasound effects. Data suggested that for lipophilic betaxolol ultrasound-induced convection was the dominant mechanism in enhancing drug penetration. For less lipophilic timolol and carteolol, permeability enhancement was likely caused by both convection and epithelial damage.

\textbf{INTRODUCTION}

Drug delivery into the eye is a significant clinical problem. Systemically administered drugs have poor access due to the blood-aqueous barrier, which prevents drugs from entering into the aqueous humor, and the blood-retina barrier, which prevents drugs from entering into the extravascular space of the retina and into the vitreous body. Topically applied drugs are rapidly eliminated from the corneal surface due to the tear rinsing. The removed drug is then absorbed into the systemic circulation, increasing the possibility of systemic adverse effects.

Although the cornea is considered a major pathway for penetration of topically applied drugs, it is still a significant barrier. It consists of 3 primary layers: epithelium, stroma, and endothelium. For hydrophilic drugs, the epithelium presents the dominant barrier to drug penetration, and the stroma is the main barrier for lipophilic drugs.

It has been shown that the barrier properties of cornea can be changed by the application of physical methods like iontophoresis (application of electrical current) and sonophoresis (ultrasound application) \cite{1}. Sonophoresis at frequencies of 660-880 kHz and intensity of 0.2 W/cm\textsuperscript{2} applied for 5 minutes produced up to 10 times increase in the cornea permeability in rabbit model \textit{in vivo} \cite{2, 3, 4}. The mechanism of action was thought to be cavitation-induced cornea epithelium damage that healed in 6 hours \cite{3}.

The objective of our work was to determine whether 20 kHz ultrasound, which was shown to be effective in transdermal drug delivery \cite{5}, can increase corneal permeability for different glaucoma drugs.

\textbf{METHODS}

The diffusion of 3 glaucoma drugs, carteolol, timolol, and betaxolol, was measured across the isolated rabbit cornea using a vertical two-chamber glass diffusion cell. The cornea was positioned such that the epithelial layer was facing the donor compartment, which was filled with the ophthalmic drug solution. The receiver compartment was filled with phosphate-buffered saline (PBS, pH 7.4). The cornea was exposed to the ophthalmic solution for 60 min. Ultrasound was simultaneously applied with an exposure duration of 10, 30 and 56 minutes corresponding to ultrasound energy doses of 1200, 3600 and 6720 J/cm\textsuperscript{2}, respectively.

In one set of experiments, ultrasound was applied for 56 min from the donor chamber filled with PBS. After the ultrasound was turned off, the donor chamber was filled with the drug solution and left for 60 min. This was done to distinguish immediate from long-term ultrasound effects.

The solution sample was taken from the receiver compartment after the experiment and the drug concentration was measured with a spectrophotometer (UV-1601, Shimadzu). The ratio of drug concentration in the receiver compartment after control and treatment experiments was used to quantify the change in corneal permeability.

Ultrasound was applied using a sonicator (VCX 500, Sonics) operating at 20 kHz frequency. The ultrasound transducer tip was positioned at 0.5 cm distance from the cornea. The duty cycle was 14.3% (1 s on time, 6 s off time). A calorimetric method was used to measure ultrasound intensity \cite{5}. The spatial-average pulse-average intensity (\textit{I}_{SPA}) was 14.3
W/cm², and the spatial-average temporal-average intensity (IsATA) was 2 W/cm².

Drug transport through the cornea was dependent on temperature. Therefore, a thermal bath was used to produce similar temperature changes (23-35.6 °C) in all experiments as achieved in treatment experiments at exposure duration of 56 min.

RESULTS

When ultrasound was applied with an average intensity of 2 W/cm² and exposure duration of 56 minutes, the permeability increased by 2.5 times for carteolol, 1.8 times for timolol and 4.8 times for betaxolol (p<0.05 for all 3 drugs). Permeability increase was also observed as a function of ultrasound energy dose (Fig. 1).

The drug concentration in the receiver compartment after the experiments is shown in Table 2 for the case when the ultrasound (US) and the drug solution were applied separately (Column 3) and when applied together (Column 2).

Ultrasound at 2 W/cm² applied for 56 min appeared to produce structural changes in the corneal epithelium and stroma (Fig. 2). The epithelium was partially detached, and bubble-like structures appeared to be present in both the epithelium and the stroma.

DISCUSSION AND CONCLUSION

The results showed that 20 kHz ultrasound increased corneal permeability for all 3 drugs when applied simultaneously with the drugs. When ultrasound and the drug were applied separately, no permeability increase was achieved for betaxolol. Some increase was achieved for timolol (p=0.07) and carteolol (p=0.14) (Table 1). It appears that for lipophilic betaxolol, ultrasound-induced convection played the dominant mechanism in enhancing drug penetration through the cornea. For less lipophilic timolol and carteolol, permeability enhancement was likely caused by both convection and epithelial damage.

It has been shown previously that damaged epithelium healed in 6 hours after the application of 880 kHz ultrasound at 0.2 W/cm² [3]. Further investigation is needed to determine the reversibility of structural changes in the cornea caused by 20 kHz ultrasound. Ultrasound may provide a valuable method for drug delivery into the eye.

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A New Synthetic Tissue-Mimicking Phantom For High Intensity Focused Ultrasound


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To study the bioeffects and dosimetry of High Intensity Focused Ultrasound (HIFU), experiments are usually carried out on biological tissues. However, this choice presents several difficulties: 1) tissues are opaque and development of coagulative necrosis lesions cannot be easily visualized in real-time, and 2) tissues have a heterogeneous structure and comparison with numerical model results that assume homogenous tissue structure may not be straightforward. While many tissue-mimicking phantoms have been developed for ultrasound imaging applications, none are available for exploration of the high temperature and pressure regimes involved in HIFU. We have developed an optically transparent, poly-acrylamide gel-based tissue phantom with physical and acoustic properties similar to those of soft tissue (sound speed approximately 1540 m/s, density approximately 1045 kg/m$^3$). The phantom includes a thermally sensitive indicator protein (Bovine Serum Albumin, 3 – 9%) that becomes optically diffusive when denatured. The acoustic attenuation in the phantom varies significantly with BSA concentration (attenuation slope ranging between 0.009 and 0.020 Np/cm/MHz). While the higher BSA concentrations facilitated the visualization of thermal effects of HIFU (focal opacification), the lower concentrations demonstrated the cavitation activity (vivid bubble activity).

**INTRODUCTION**

The extent of damage during High Intensity Focused Ultrasound (HIFU) treatment must be highly controlled, especially in sites in which important healthy structures are close to the targeted zone. If an image guided monitoring system is not available to plan the treatment in real time, a thorough preliminary dosimetry study is essential. To study the bioeffects of HIFU, experiments are usually performed on biological tissues [1]. However, tissues are opaque and the development of coagulation necroses cannot be observed in real time. The observation of lesion dynamics requires a multitude of “time lapse” experiments, varying the exposure dose and recording the corresponding bioeffects. Furthermore, tissues have heterogeneous structure, leading to some variability. Theoretical simulations of HIFU exposure usually assume homogeneous media. Thus, the comparison between experimental observations and theoretical predictions may not be straightforward.

Many phantoms have been devised to mimic tissues exposed to an ultrasound field, most of which are for imaging applications [2]. None of these phantoms is suitable for exploration of the high temperature and pressure regimes involved in HIFU exposures. The ideal phantom material must have several new properties. First, the material should match biological tissues acoustically and thermally. For real-time observation of HIFU-induced lesions evolution, the optical transparency of the phantom in its pretreated state is necessary. Also, the phantom must change in a permanent, localized, and observable way in response to HIFU heating. Though perfusion of tissue can dissipate heat, the effect can often be neglected for HIFU applications away from larger vessels for less than 2 seconds. In the present study, a new tissue-mimicking phantom for studying HIFU dosimetry is presented and characterized acoustically.

**METHODS**

**Gel fabrication**

This tissue-mimicking phantom is based on a polyacrylamide gel mixed with Bovine Serum Albumin (BSA), a protein used here as a temperature-sensitive indicator. A 7% acrylamide solution is made from commercial 40% stock solution and degassed water. Preliminary experiments determined suitable BSA concentrations: while too much BSA results in a non-transparent (diffusive) gel, too little BSA results in low sensitivity and low optical contrast. A BSA concentration between 3 and 9% (by mass) is satisfactory for visualization of HIFU exposures.

**Gel acoustic characterization**

The gel density is obtained from measurements of the mass and the volume of a tested sample. The technique and the equipment used give an error of less than 5%. A pair of PVDF transducers is used to measure acoustic attenuation and sound velocity. The approach is to make transmission measurements of an
acoustic signal through the tested sample and compare the received signal with one transmitted through a reference water path with the same geometry. Six samples are tested for each concentration. The sound speed is measured at 1 MHz and the attenuation between 1 and 5 MHz. A 7% BSA concentration sample is also immersed in a thermo-regulated water bath to determine the temperature dependence of both parameters. The error for each measurement of each parameter is less than 10%.

RESULTS

The density and the sound speed are independent of BSA concentration in the range of 3 to 9%. The density of the phantom is 1044 ± 15 kg/m³, the sound speed is 1544 ± 11 m/s (Average ± Standard deviation, N = 24). The attenuation is essentially linear over the studied frequency domain (Fig. 1). The slope of the trend line increases with the BSA concentration. It ranges between 0.009 and 0.020 Np/cm/MHz. The attenuation is unchanged, even with an extra degassing of the unpolymerized mixture, indicating that dissolution of BSA does not seem to add many micro-bubbles. The sound speed has a temperature dependence very similar to that of water, with a maximum of 1590 m/s near 50°C (Fig. 2). The attenuation shows an opposite trend with a minimum near 50°C (Fig. 3). The inverted variation of the attenuation is reminiscent of the relative trends in the frequency domain that are a consequence of the Kramers-Kronig relationship [3].

DISCUSSION AND CONCLUSIONS

The new material based on poly-acrylamide gel and BSA protein is a useful phantom for visually modeling HIFU lesion formation in biological soft tissues in terms of the linear acoustic parameters: density, sound speed, and attenuation. The attenuation can be adjusted by changing the BSA concentration, and it may be possible to increase the concentration beyond 9% to reach attenuation values of typical soft tissues while maintaining adequate optical clarity.

The transparent nature of this phantom for the selected range of BSA concentrations permits real time observation of HIFU-induced lesions. Figure 4 presents an image of two lesions created in a gel block with a BSA concentration of 7%. At higher power the lesion grows toward the transducer (off the image to the left side) and loses its symmetrical “cigar” shape (lesion B obtained at low power). Low BSA concentration results in visible bubble activity while larger concentrations emphasize a thermal regime.

In conclusion, this new phantom is a promising tool to study HIFU dosimetry. The next step will be to determine the thermal characteristics of this phantom.

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