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Overview of Therapeutic Ultrasound Applications and Safety Considerations

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Summary

Applications of ultrasound in medicine for therapeutic purposes have been an accepted and beneficial use of ultrasonic biological effects for many years. Low power ultrasound of about 1 MHz frequency has been widely applied since the 1950s for physical therapy in conditions such as tendinitis or bursitis. In the 1980s, high pressure-amplitude shockwaves came into use for mechanically resolving kidney stones, and “lithotripsy” rapidly replaced surgery as the most frequent treatment choice. The use of ultrasonic energy for therapy continues to expand, and approved applications now include uterine fibroid ablation, cataract removal (phacoemulsification), surgical tissue cutting and hemostasis, transdermal drug delivery, and bone fracture healing, among others. Undesirable bioeffects can occur including burns for thermal-based therapies and significant hemorrhage for mechanical-based therapies (e. g. lithotripsy). In all these therapeutic applications for bioeffects of ultrasound, standardization, ultrasound dosimetry, benefits assurance and side-effects risk minimization must be carefully considered in order to insure an optimal benefit to risk ratio for the patient. Therapeutic ultrasound typically has well-defined benefits and risks, and therefore presents a tractable safety problem to the clinician. However, safety information can be scattered, confusing or subject to commercial conflict of interest. Of paramount importance for managing this problem is the communication of practical safety information by authoritative groups, such as the AIUM, to the medical ultrasound community. In this overview, the Bioeffects Committee outlines the wide range of therapeutic ultrasound methods, which are in clinical use or under study, and provides general guidance for assuring therapeutic ultrasound safety.

Introduction

Ultrasound has seen development not only as a diagnostic imaging modality but as a therapeutic modality in which energy is deposited in tissue to induce various biological effects. Medical uses of ultrasound for therapy began to be explored in the 1930s. Early applications were tried for various conditions using the mechanism of tissue heating (Lehmann, 1953). Over the following decades, scientific advances allowed improved methods for effective treatment of Meniere’s disease by destruction of the vestibular nerve, and of Parkinson’s disease using focused ultrasound for localized tissue destruction in the brain (Fry et al. 1954; Newell, 1963). By the 1970’s, the use of therapeutic ultrasound was established for physiotherapy, and research continued on more difficult applications in

neurosurgery (Wells, 1977), and for cancer treatment (Kremkau, 1979). Subsequently, the development of therapeutic ultrasound has accelerated with a wide range of methods now in use. The potent application of ultrasound for therapeutic efficacy also carries the risk of unintentional adverse bioeffects which can lead to significant, even life threatening patient injury. Therefore, standardization, ultrasound dosimetry, benefits assurance and side-effects risk minimization must be carefully considered in order to insure an optimal outcome for the patient.

The purpose of this review is to briefly outline the recent development of therapeutic ultrasound applications and specialized devices, which have been approved for use, together with associated safety considerations. Therapeutic applications of ultrasound may be used clinically after government approval (e. g. by the Food and Drug Administration (FDA) in the United States) for marketing suitable treatment devices. A list of therapy applications with FDA approved devices in clinical use is provided in Table 1. The fundamental basis behind the ultrasound mediated deposition of energy and mechanisms for biological effects are discussed. This is followed by a discussion of ultrasound treatment methods using heating, which include physical therapy, hyperthermia and high-intensity focused ultrasound. Nonthermal applications are then reviewed, including extracorporeal shock wave lithotripsy, intracorporeal lithotripsy and lower power kilohertz frequency ultrasound devices. Some ultrasound therapy methods have uncertain, possibly multiple mechanisms, including skin permeabilization for drug delivery and low-intensity pulsed ultrasound, which can accelerate the healing of bone fractures. Prospective new methods of therapeutic ultrasound are mentioned at the end, including new microbubble- or cavitation-based treatment methods. Lastly, the reader is reminded about important safety considerations and general guidelines are presented. There is no doubt that continued biophysical discoveries in ultrasound will lead to new treatments and applications. As therapeutic ultrasound's renaissance continues, new treatments already well established in the laboratory will be translated in the near future to the clinic.

The Biophysical Bases for Therapeutic Ultrasound Applications

Ultrasonic energy can be a potent modality for generating biological effects. Given sufficient knowledge of the etiology and exposimetry, bioeffects can be planned for therapeutic purposes or avoided in diagnostic applications. For therapy, ultrasound can induce effects not only through heating, but also through nonthermal mechanisms including ultrasonic cavitation, gas body activation, mechanical stress or other undetermined nonthermal processes (Nyborg et al. 2002).

Starting from the diagnostic reference frame, ultrasound is usually produced from a piezoceramic crystal in very short, i.e., 1- to 5-cycle, pulses. Diagnostic ultrasound is often characterized by the center frequency of the pulses (typically in the 2–12 MHz range), which is usually a frequency inherent to the thickness of the ceramic crystal. As the pressure amplitude, the frequency, or the propagation length is increased, the ultrasound wave can distort, which could ultimately lead to a discontinuity or shock in the waveform. In regard to bioeffects, increasing frequency, nonlinear acoustic distortion, or pulse length can increase heating and enhance some nonthermal mechanisms, e.g., radiation force. Decreasing frequency increases the likelihood of cavitation and gas body activation. Increasing power or intensity tends to increase the likelihood and magnitude of all bioeffects mechanisms. Therapeutic ultrasound devices may use short bursts or continuous waves to deliver effective ultrasonic energy to tissues. Some devices operate at higher amplitude and therefore tend to produce shocked or distorted waves.

Ultrasound-induced heating is the result of the absorption of ultrasonic energy in biological tissue. For diagnostic ultrasound, temperature elevations and the potential for bioeffects are kept relatively low or negligible (Fowlkes et al. 2008) by carefully described indications for use, applying the ALARA (as low as reasonably achievable) principal, limited temporal average intensities, and generally short exposure durations. Therapeutic applications of ultrasonic heating therefore either utilize longer durations of heating with unfocused beams, or utilize higher intensity (than diagnostic) focused ultrasound. The use of unfocused heating, for example in physical therapy to treat highly absorbing tissues such as bone or tendon, can be moderated to produce enhanced healing without injury. Alternatively, the heat can be concentrated by focused beams until tissue is coagulated for the purpose of tissue ablation. Ultrasound heating which can lead to irreversible tissue changes follows an inverse time-temperature relationship. Depending on the temperature gradients, the effects from ultrasound exposure can include mild heating, coagulative necrosis, tissue vaporization, or all three.

Ultrasonic cavitation and gas body activation are closely related mechanisms which depend on the rarefactional pressure amplitude of ultrasound waves. Ultrasound transmitted into a tissue may have rarefactional pressure amplitudes of several megaPascals (MPa). This tensile stress is supported by the medium and, for example, a 2-MPa rarefactional pressure, which is common even for diagnostic ultrasound, represents a negative tension 20 times atmospheric pressure (i. e., 0.1 MPa). This high rarefactional pressure can act to initiate cavitation activity in tissue when suitable cavitation nuclei are present, or directly induce pulsation of pre-existing gas bodies, such as occur in lung, intestine, or with ultrasound contrast agents. Cavitation and gas body activation primarily cause local tissue injury in the immediate vicinity of the cavitation activity, including cell death and hemorrhage of blood vessels.

Other potential mechanisms for biological effects of ultrasound include the direct action of the compressional, tensile, and shear stresses. In addition, second-order phenomena, which depend on transmitted ultrasound energy, include radiation pressure, forces on particles and acoustic streaming. For high-power or high-amplitude ultrasound for therapy, several different mechanisms may be contributing concurrently to the total biological impact of the treatment. In addition to direct physical mechanisms for bioeffects, there are secondary physical, biological, and physiological mechanisms that cause further impact on the organism. Some examples are vasoconstriction, ischemia, extravasation, reperfusion injury, and immune responses (e.g., Alves et al. 2009, Hundt et al. 2007, Silberstein et al. 2008). Sometimes these secondary effects are greater than the direct insult from the ultrasound.

Therapeutic Applications of Ultrasound Based on Heating

Physical Therapy

Unfocused beams of ultrasound for physical therapy were the first clinical application, dating to the 1950s, which often has been referred to simply as “therapeutic ultrasound” (Robertson and Baker, 2001). This modality now typically has a base unit for generating an electrical signal and a hand-held transducer. The hand-held transducer is applied with coupling gel and moved in a circular motion over an injured or painful area of the anatomy to treat conditions such as bursitis of the shoulder or tendonitis, by trained physical therapy technicians. The objective is to warm tendons, muscle and other tissue to improve blood flow and accelerate healing. The coupling medium can also include various compounds for enhancing the treatment. Ultrasound application can also assist by promoting transport of the compound into the skin, a method sometimes called sonophoresis or phonophoresis (as opposed to electrophoresis) (Machet and Boucaud, 2002). Drugs such as lidocaine or cortisol have been used extensively in sports medicine. The level of clinical benefit to the

patient from physical therapy ultrasound treatments remains uncertain (Robertson and Baker, 2001; Baker et al. 2001; Alexander et al. 2010). However, the risk of harm such as burns, appears to be low when the modality is properly applied. Overall, ultrasound for physical therapy has therefore provided a modest level of efficacy and patient benefit, but also a low level of risk.

Hyperthermia

A substantial effort during the 1980s and 1990s sought to develop means to ultrasonically heat relatively large volumes of tissue for the purpose of cancer therapy. This method of hyperthermia involves uniformly heating a tumor to about 42 °C for periods of about 1 hour, which appears to be effective in reducing tumor growth (Sapareto and Dewey, 1984). Multi-element applicators have been used at 1–3.4 MHz (Samulski et al. 1990; Diederich and Hynynen, 1999). In clinical trials, hyperthermia was used with or without radiation therapy and modest efficacy has been reported (Marchal, 1992). Research suggests that hyperthermia may be advantageous for drug delivery treatment using nanoparticles (Kong et al. 2000). However, the moderate-temperature hyperthermia method has not progressed to widespread clinical usage, and the effort in hyperthermia cancer treatment has shifted to the use of high intensity focused ultrasound.

High Intensity Focused Ultrasound

High intensity focused ultrasound (HIFU, or HIFUS) was initially studied clinically for thermal ablation of inoperable brain tissue for Parkinson's disease (Fry et al. 1954; Kennedy et al. 2003). In a HIFU system, a signal generator is connected to a focusing transducer, which produces very high local intensities of $>1 \text{ kW/cm}^2$ of 0.5–7 MHz ultrasound at the focal spot. The lesion produced in tissue typically may be a few mm in diameter and in length. The position of this spot must be carefully controlled and moved in order to ablate larger volumes of tissue. This method is approved by the FDA in the USA for treating uterine fibroids (Tempany et al. 2003), cardiac ablation (Ninet et al. 2005), visceral soft tissue ablation (Klingler et al. 2008), and aesthetic treatment to lift the eyebrow (Gliklich et al. 2007; Alam et al. 2010). In addition, a method was developed and was approved for treatment of glaucoma using HIFU (Burgess et al. 1986).

In addition to the devices approved by the FDA for clinical use, there are several procedures that are being investigated for clinical application (Evans et al. 2007). HIFU application in therapy and treatment of disease is one of the more active areas of research and development among all the non-ionizing-energy modalities such as radiofrequency, lasers, and microwaves. For example, HIFU is under investigation for therapeutic modulation of nerve conductance (Foley et al. 2008). Among other applications, the oldest and possibly the most investigated area (particularly outside the USA) is the treatment of benign prostatic hyperplasia (BPH) and the treatment of prostate cancer using HIFU. A number of multi-center and systematic studies with several-year follow up has established the use of HIFU as a viable option for the management of prostate cancer (Gelet et al. 2000; Thüroff et al. 2003).

A key element of therapeutic applications with ultrasound energy is the capability to focus energy several millimeters to centimeters away from the transducer plane. It is therefore, very important to accurately determine the location of the treatment zone with ultrasound systems. Further, the tissue changes in the treatment zone must be reliably monitored, in order to confirm that adequate treatment has been achieved. The focused ultrasound beam can then be moved to a different location to complete the treatment of the planned volume. Two methods used for image guidance and treatment monitoring are magnetic resonance imaging (MR) and ultrasound imaging. MR imaging can measure temperature changes

during therapy, within the treatment zone of therapeutic ultrasound procedures (Jolesz, 2009). Specialized clinical systems have ultrasound therapy sub-systems integrated into MR-imagers, which are used for uterine fibroid treatment (Tempany et al. 2003), breast cancer (Gianfelice et al. 2003), and prostate cancer management (Chopra et al. 2009). Ultrasound based guidance and monitoring offers the possibility of systems that incorporate both the treatment and imaging modality in one compact system. The ultrasound image monitoring of tissue changes during ultrasound therapy is based on a combination of speed of sound, attenuation, stiffness, and vapor content changes in the target region (Fedewa et al. 2006, Larrat et al. 2008), including boiling detection and combined measurement and modeling approaches Anand and Kaczkowski, 2009; Canney et al. 2010).

In addition to external focused devices, a number of other devices and systems are being developed for soft tissue coagulation which are primarily used in non-invasive approaches, or through natural orifices such as the transrectal approach for prostate treatments (Makin et al. 2005). For example, transurethral ultrasound has been proposed for heating the prostate (Kinsey et al. 2008; Chopra et al. 2009), and endoscopic treatment using an intraductal ultrasound probe has been used to treat bile duct tumors (Prat et al. 2002).

Significant research and development are being pursued in the area of non-invasive aesthetic applications. Focused ultrasound in these applications is directed within the first 2 – 20 mm of the skin and subcutaneous tissue (dermis – subcutaneous fat). Very small lesions of ~1 mm³ up to several 10s of cm³ can be produced. The approach may provide a safer alternative to liposuction for cosmetic applications (Moreno-Morega et al. 2007). Superficial tissue is exposed to HIFU leading either to a contraction of collagen based tissue (dermis) or to destruction of adipose tissue (Gliklich et al. 2007; White et al. 2007). A clinical system has been approved for fat debulking in the European Union and Canada (Fatemi, 2009). Depending on the device, as well as the cosmetic application, both thermal as well as non-thermal mechanisms within an ultrasound field are employed for these procedures. One of these devices is currently approved for clinical use in the USA (Alam et al. 2010), and others are in use worldwide. Long term utilization of this technology, as well as regulatory approval, is still evolving.

HIFU applications involve delivery of substantial ultrasonic energy to localized areas, and undesired tissue injury is always a consideration. Typically, unwanted burns and pain can occur. In addition, HIFU can cause vasospasm and hemorrhage under conditions which generate concomitant cavitation in tissue (Hynynen et al. 1996). Other significant bioeffects and complications can also occur with unique risk-benefit considerations for each application. Treatment of the prostate, such as for prostate cancer, can lead to several urologic complications, including impotence and incontinence (Rove et al. 2010), which can also accompany other types of treatment for prostate cancer. HIFU has been used to treat atrial fibrillation by tissue ablation to produce pulmonary vein isolation. However, severe complications can occur due to creation of an atrial-esophageal fistula (Borchert et al. 2008), a concern which is difficult to eliminate (Neven et al. 2010). Treatment of hepatic and pancreatic cancer can also lead to serious complications, including fistula formation and rib necrosis with delayed rib fracture (Jung et al. 2010). Detailed safety considerations should accompany the introduction of HIFU applications into clinical practice in order to assure benefit, while minimizing risk to the patient.

Therapeutic Applications of Ultrasound Based on Non-Thermal Mechanisms

Extracorporeal Shock Wave Lithotripsy

Extracorporeal shockwave lithotripsy (ESWL) is a widely used ultrasound therapy, which relies on nonthermal mechanisms for its efficacy (McAteer et al. 2005; Weizer et al. 2007). When introduced in the 1980s, lithotripsy gained rapid acceptance and became the dominant treatment method. Shock wave devices similar to lithotripters are approved and marketed for orthopedic indications such as plantar fasciitis and epicondylitis (Haake et al. 2003). The use of shockwaves for treating other problems, such as gall bladder stones, has also been explored, but none have achieved widespread usage. Over 50 lithotripter devices have been on the USA market. Fluoroscopy is used for targeting the acoustic focus on the stone in the USA, although some lithotripters have B-mode ultrasound for targeting. The first lithotripters were electrohydraulic, using an underwater spark source and a reflector. Most lithotripters now are of the electromagnetic design, which deposits a high transient current through a coil that in turn produces a displacement of a plate. Very few lithotripters utilize piezoceramic sources. All produce about the same waveform: a 1- μ s shocked spike of about 50 MPa followed by a ~10-MPa, 4- μ s negative pressure tail. The center frequency might be estimated to be about 150 kHz although this is not a commonly determined parameter. There was a trend to more focused machines, relative to early spark gap models, but that has fallen out of favor. Evidence has been presented for a reduction in clinical effectiveness and safety for highly focused shockwaves (McAteer et al. 2005), and for the dependence of fragmentation mechanisms on beam width (Eisenmenger, 2001; Sapozhnikov et al. 2007).

For ESWL treatment, the source is coupled to the patient by a water pillow and transmission gel, and in the remaining original lithotripters through a water bath. Coupling has recently been recognized as a significant factor in ESWL treatment efficacy; a point that has implications across therapeutic ultrasound (Pishchalnikov et al. 2006). About 3000 shock waves are triggered at about 2 Hz repetition rate to pulverize the stone so that the pieces (<2mm) can pass naturally in urine. The prominent mechanism is the wave running over the stone creating shear waves to tear the stone apart from within. Cavitation chips away from the outside, adding cracks that grow by dynamic fatigue and further grind down the stone to passable size (Sapozhnikov et al. 2007).

Lithotripsy has several important biological side effects. Lithotripsy causes injury to virtually all patients (Evan and McAteer, 1996). Blood vessel walls break, and there is bleeding into the connective tissue interstitium, which can result in bruising of the parenchyma or the formation of massive subcapsular hematomas. Inflammation ensues (i.e. lithotripsy nephritis), which can lead to scar formation (Koga et al. 1996) and permanent loss of functional renal mass (Evan et al. 1998). In addition to and likely a result of this direct injury cascade, lithotripsy can lead to an accelerated rise in systemic blood pressure, a decrease in renal function, onset of hypertension, an increase in the rate of stone recurrence, and an exacerbation of stone disease (Janetschek et al. 1997; Krambeck et al. 2010). A single retrospective study has linked lithotripsy and diabetes mellitus (Krambeck et al. 2006).

The risks of these adverse bioeffects in lithotripsy have stimulated investigation into mitigation methods with some success (McAteer et al. 2005). For example, a slower repetition rate (1 Hz) is safer and more effective than the common fast rate (2 Hz) (Pace et al. 2005), and a pause early in treatment nearly eliminates injury in animals (Weizer et al. 2007; Handa et al. 2009). Overall, lithotripsy has been a therapeutic ultrasound method with a high level of efficacy and patient benefits, but also some important risks particularly for

patients requiring repeated treatments. The development of safer treatment protocols for lithotripsy is a prime example of the potential value of research on risk mitigation for optimizing the patient risk/benefit profile in therapeutic ultrasound.

Intracorporeal lithotripsy

Lithotripsy is also accomplished by minimally invasive probes which are advanced to the stone. Intracorporeal lithotripsy is the favored treatment for many patients, for example for very large stones, and many different methods and techniques have been reported. The stone may be imaged for guidance by external ultrasound or fluoroscopy, or by ureteroscopic, endoscopic or laparoscopic methods. Rigid probes may be manipulated percutaneously, but some flexible probes can be applied via the ureter. Rigid ultrasonic probes can utilize both pneumatic action at a few Hz to 1,000 Hz, and ultrasonic action at about 25 kHz (Kim et al. 2007; Lowe and Knudsen, 2009). Electrohydraulic probes, which generate a vaporous cavity at the tip (similar to the spark gap external lithotripter but without focusing) (Noor Buchholz, 2002), have been used in the past. Intracorporeal lithotripsy carries risk of hemorrhage, ureteral perforation, urinary tract trauma, and infection due to the invasive nature of the procedures.

Kilohertz-Frequency Ultrasound Devices

Ultrasonic systems operating in the kHz-frequency regime (20 – 90 kHz), similar to “sonicators” used in biological research to break up cells and tissues, are used routinely in general and advanced surgical procedures for tissue cutting and hemostasis as well as for tissue removal. These appear to act primarily through localized biophysical effects close to the probe tip, rather than via radiated ultrasound waves. For example, a kHz-frequency ultrasound probe is used for phacoemulsification to remove the lens of the eye during surgery for cataracts (Packer et al. 2005). The probe appears to mechanically chop up the lens, possibly aided by ultrasonic cavitation, with the lens debris removed by suction through the probe. The procedure is well established in ophthalmology and minimizes the impact on the lens capsule.

Surgical ultrasonic instruments, known as “harmonic scalpels”, have a 40 – 80 kHz vibrating titanium rod with a static clamp member, between which the tissue (and blood vessels) is rapidly coagulated due to localized frictional heating (Koch et al. 2002). Another procedure, ultrasound assisted liposuction, is widely used in cosmetic surgery for the purpose of removing excessive fat tissue (Mann et al. 2008). The mechanism of action apparently involves cavitation fat cell break up with removal of the fat emulsion by suction through the probe. This procedure is invasive, and can lead to complications such as bleeding, scarring and infection.

Therapeutic Applications of Ultrasound with Multiple Mechanisms

Catheter Based Ultrasound

Intravascular catheters have been developed with MHz-frequency ultrasound transducers placed near the tip for enhancing dissolution of thrombi (Parikh et al. 2008). The catheter is placed into a deep vein thrombus and the ultrasound is directed radially into the thrombus. In addition, there are provisions for infusion of thrombolytic drugs, such as tissue plasminogen activator. The ultrasound accelerates the action of the thrombolytic drugs so that the total infusion dose of drugs and treatment times can be reduced significantly. The role of this method, and the full range of its clinical usefulness for thrombolysis is still being evaluated.

Skin Permeabilization

For transdermal drug delivery, the *stratum corneum* ($\approx 10\text{--}30\ \mu\text{m}$) forms a barrier to passive drug diffusion for molecules which have a weight greater than 500 Da (Boucaud 2004). One effect of low-frequency ultrasound ($<100\ \text{kHz}$) is its ability increase permeability of the *stratum corneum*, which is considered to be a primary barrier to protein diffusion (Pitt et al. 2004; Mitragotri and Kost 2004). The treatment can be monitored by measuring the electrical skin conductance (Farinha et al. 2006). Once a drug has traversed the *stratum corneum*, the next layer is easier to cross and subsequently the drug can reach the capillary vessels to be absorbed (Mitragotri et al. 1995). This skin permeabilization method may be useful for avoiding the multiple use of needles, for example, for delivery of heparin or insulin through the skin (Smith, 2008).

Low Intensity Pulsed Ultrasound

Low intensity pulsed ultrasound has therapeutic application to accelerate the healing of bone fractures including cases of nonunion (Gebauer et al. 2005). The characteristics of the pulsed ultrasound, for example, 1.5-MHz frequency with 30-mW/cm^2 spatial average temporal average intensity, are in the range of diagnostic ultrasound. The biophysical mechanisms for the therapeutic action are uncertain for this application. Therapy involves multiple treatments of 20 min each day by applying the large flat transducer to the site of injury and continuing treatment for periods of months. Although the process appears to be safe and effective, the therapy is slow and its use is predominantly limited to management of non-healing fractures.

Prospective New Methods of Therapeutic Ultrasound

In this era of ultrasonics research, several new means of applying ultrasound for therapy are undergoing intensive research and development. The novel methods utilize low frequency, moderate power ultrasound aided by stabilized microbubbles for gas body activation, or very high power pulsed ultrasound with vigorous cavitation.

Direct sonothrombolysis using external, typically low frequency ultrasound has been tested for treatment of thrombotic disease, such as stroke (Siegal and Luo, 2008). This new strategy shows promise, but also has shown a potential for deleterious side effects. For example, increased brain hemorrhage was found in a clinical trial for treatment with 300 kHz ultrasound plus tissue plasminogen activator relative to treatment with tissue plasminogen activator alone (Daffertshofer et al. 2005). Recent work suggests that microbubbles enhance thrombolysis and may be of value in improving stroke therapy (Hitchcock and Holland, 2010).

Another potential application in brain utilizes transcranial pulsed ultrasound (0.25 – 0.5 MHz), at relatively low levels ($I_{\text{SPTA}} = 26\text{--}163\ \text{mW/cm}^2$), to produce cortical and hippocampal stimulation in mice (Tufail et al. 2009). Since measured temperature gradients were $<0.01^\circ\text{C}$, nonthermal mechanisms for the neuronal effects were hypothesized.

Microbubble-based therapeutic strategies are under study for ultrasound directed and targeted therapy. In these strategies, the external ultrasound exposure activates microbubbles in the circulation, which may also act as drug carriers, at a desired site of treatment. Microbubble contrast agents have also found applications in improving the therapeutic efficacy of biologically active molecules (Tinkov et al. 2009). Several possible mechanisms include the enhancement of (1) the concentration of therapeutic biomolecules in the vascular compartment of the target area, (2) increased therapeutic agent delivery by extravasation through blood vessels, and (3) potentially enhanced intracellular delivery. Molecules of the therapeutic agent can be attached to the outer shell of bubbles, incorporated within the

bubble shell or loaded into the interior of microbubbles and released in the vascular compartment through ultrasound-induced microbubble disruption (Unger et al. 2004; Ferrara et al. 2007). The extravasation of a therapeutic agent is achieved through the permeabilization of blood vessels with ultrasound and microbubbles, for example, to cross the blood-brain barrier (Vykhodtseva et al. 2008). The ultrasound-microbubble based delivery of therapeutic agents has one main advantage over other techniques using colloidal drug carriers such as nanoparticles or liposomes: The microbubble-based technique may be targeted through the external control of the ultrasound. This localized approach may then improve the therapeutic efficacy of drugs, such as routinely used chemotherapeutic agents like paclitaxel. The dose of agent to normal tissue is lowered, with a consequent minimization of unwanted drug effects away from the treatment site (Tartis et al. 2006). At the cellular level, ultrasound with microbubbles can be used to transiently permeabilize cell membrane, allowing transfer of large molecules into the cells. DNA transfer has been demonstrated in extensive research on gene therapy applications (Miller, 2006).

The cavitation mechanism is also being exploited to create a new tissue-ablation method known as histotripsy (Kieran et al 2007). In histotripsy (akin to lithotripsy pulses but at a higher frequency), very high amplitude ultrasound pulses typically of less than 50 μ s duration at 750 kHz create a cavitation microbubble cloud to homogenize targeted tissue such as tumors with little heating (Xu et al. 2008). Longer HIFU pulses (e. g. >3 ms at 2 MHz) of very high intensity can induce rapid heating and also generate cavitation and boiling with vapor bubbles that expand very rapidly, thus disrupting tissue (Canney et al. 2010).

Because cavitation is a mechanism secondary to the ultrasound exposure, the problems of dosimetry and control are challenging. Determining the energy deposited by ultrasound with cavitation is difficult under the best of circumstances (Apfel 1981; Hamilton and Blackstock, 1998). For cavitating ultrasound, researchers try to follow three rules: (i) understand the medium (including cavitation nuclei), (ii) understand the sound field and (iii) know when a cavitation effect happens (Apfel 1981). The first rule refers to the cavitation threshold while the second rule relates to accurate measurements of the acoustic field. The third relates to observable cavitation events or secondary related information which can be monitored. There are various reliable and scientifically established methods for quantifying an acoustic field (Lewin and Ziskin 1992; Harris 2005; Shaw and ter Haar 2006; Shaw and Hodnett 2008). Passive detection methods, measuring broadband acoustic noise from bubble collapses for monitoring cavitation activity can be deployed and research has indicated useful dosimetric parameters which may be derived for predicting bioeffects (Hwang et al. 2006). As new cavitation-based treatments are developed, new means for cavitation dosimetry and control will be needed to assure optimum patient safety.

General Guidance for Therapeutic Ultrasound Safety

Therapeutic ultrasound methods provide a substantial armamentarium for medical practice. In addition, ultrasound brings fundamentally favorable safety characteristics to the clinic. For example, ionizing radiation with its dose accumulation and cancer risk is absent from ultrasound methods. Low energy exposures, below the threshold for a bioeffect, do not accumulate to produce the effect, even if repeated many times. The ultrasonic waves are dispersed and poorly transmitted in air: no lead gloves, aprons or other protective gear are needed for ultrasound diagnosis or therapy. However, this powerful modality does require attention to several safety factors in order to achieve the optimum benefit to risk ratio.

Operator safety

The operator of the equipment, for the most part, has little risk of harm from the machines, can remain in the treatment room and safely apply the ultrasound with hand held applicators for some applications. However, simple precautions should be followed for complete operator safety; for example, do not test therapeutic ultrasound equipment on oneself or others (as opposed to diagnostic ultrasound imaging which can be used on volunteer models for training purposes under medical supervision).

Patient safety

Ultrasound therapy machines are, of course, capable of causing substantial bioeffects; therefore, deliberate caution must be exercised to minimize injury for each patient. Patients should be fully informed of possible risks, as well as expected benefits.

Quality assurance

Ultrasound therapy machines are typically complex and subject to deterioration or failure. Each machine should be monitored and tested on a regular basis for safe operation and verification of appropriate ultrasound fields to assure efficacious treatment.

Accumulating biological effect

Although no cumulative dose has been defined for any ultrasound therapy, unwanted bioeffects such as scarring from burns or vascular injury which occur during treatment can accumulate with repeated treatments, and this should be anticipated. For example, animal studies show permanent loss of renal functional mass with each lithotripsy and therefore recurrent treatments add injury to already compromised kidneys.

Risk benefit ratios

The benefits and potential risks associated with different therapeutic ultrasound methods vary widely and should be appreciated by the operator. For example, physical therapy ultrasound appears to have a low risk of harm in the hands of skilled physical therapists, but the expectation of therapeutic benefit is also low. Lithotripsy, in contrast, has the tremendous benefit of non-invasively treating a serious disease, which previously required major surgery, but it also has a risk of significant hemorrhage and longer-term kidney injury.

Safety Research

The search for new applications of this powerful tool should be pursued carefully, with thorough testing in appropriate animal models to identify possible human adverse events before clinical trials begin. Accurate and precise evaluation of acoustic fields in water and in situ should follow exposimetry and dosimetry procedures and numerical modeling previously recognized in the ultrasound literature. Means for monitoring heating or secondary mechanisms, such as acoustic cavitation, should be in place. Furthermore, in order to assure optimum patient benefit from therapeutic ultrasound, dedicated research should continually pursue better and safer methods to enhance present therapies and therapy monitoring.

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Table 1

A listing of FDA approved modes for ultrasound therapy.

Therapy Method	Therapeutic Outcome	Bioeffect Mechanism	Applicator	Device Characteristics			General Reference
				Frequency	Delivery	Frequency	
Unfocused beam	tissue warming	heating	portable hand-held	1–3 MHz	continuous or repeated bursts	continuous or repeated bursts	Robertson and Baker 2001
Hyperthermia	cancer therapy	regional heating	multi-element applicator	1–3.4 MHz	1 hour	1 hour	Samulski et al. 1992
HIFU	uterine fibroid ablation	thermal lesion	computer directed	0.5–2 MHz	long bursts	long bursts	Tempamy et al. 2003
HIFU	glaucoma relief	permeabilization	fixed probe with waterbath	4.6 MHz	1–3 s	1–3 s	Burgess et al. 1986
HIFU	laproscopic tissue ablation	thermal lesion	hand-held	4 MHz	long bursts	long bursts	Klingler et al. 2008
HIFU	laparoscopic or open surgery	thermal lesion	hand-held	3.8–6.4 MHz	long bursts	long bursts	Ninet et al. 2005
Focused ultrasound	skin tissue tightening	thermal lesion	hand-held, imaging and treatment	4.4–7.5 MHz	20–50 ms bursts	20–50 ms bursts	Alam et al. 2010
Extracorporeal Lithotripsy	kidney stone comminution	mechanical stress; cavitation	mainframe with image guidance	~150 kHz	shockwaves	shockwaves	Weizer et al. 2007
Intracorporeal lithotripsy	kidney stone comminution	mechanical stress; cavitation	Percutaneous probes	25 kHz	continuous	continuous	Lowe and Knudsen, 2009
Extracorporeal shockwave therapy	plantar fasciitis epicondylitis	unknown	mainframe with applicator head	~150 kHz	shockwaves	shockwaves	Haake et al. 2003
Phacoemulsification	lens removal	vibration ; cavitation	generator with probe	40 kHz	continuous	continuous	Packer et al. 2005
US assisted liposuction	adipose tissue removal	fat liquifaction; cavitation	generator with probe	20–30 kHz	continuous	continuous	Mann et al. 2008
Tissue cutting and vessel sealing	laparoscopic or open surgery	thermal lesion, vibration	hand-held	55.5 kHz	continuous	continuous	Koch et al. 2002
Intravascular US	thrombus dissolution	unknown; gas body activation	intravascular catheter	2.2 MHz	continuous	continuous	Parikh et al. 2008
Skin permeabilization	transdermal drug delivery	unknown	hand held	55 kHz	continuous	continuous	Smith, 2008
Low intensity pulsed US	bone fracture healing	unknown	attached transducer	1.5 MHz	pulsed, long duration	pulsed, long duration	Gebauer et al. 2005