

Applications and Safety of Therapeutic Ultrasound: Current Trends and Future Potential

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Abstract

The ability of ultrasound to penetrate deep into tissue and interact with human tissues via thermal and mechanical mechanisms has expanded its various therapeutic applications. In the 1950s, low power (1 MHz) ultrasound began being used for physical therapy of tendinitis or bursitis and, in the 1980s, high pressure amplitude shockwaves were used for kidney stone destruction in lithotripsy. Since then, ultrasound therapy has expanded significantly and is rapidly replacing surgery in clinics. Several major benefits of ultrasound derive from its minimally invasive procedure compared to conventional open surgeries that disturb the overlying tissues. The minimally invasive therapeutic procedures result in shortened recovery times and hospital stays as well as lowered risk of complications and cost. Ultrasound therapy may require local anesthesia or sedation, which is highly preferred over general anesthesia, especially for elderly patients. Some ultrasonic therapy techniques, such as cataract removal, surgical tissue cutting and hemostasis, transdermal drug delivery, and bone fracture healing, have been approved for widespread use. Other minimally invasive therapy techniques, such as focused ultrasound beam therapy for coagulating tissue, are on the verge of clinical approval. Therapeutic ultrasound methods work based on thermal or non-thermal (e.g., mechanical) mechanisms, or both, with well-defined benefits and risks that include complications to the patient. Ensuring the benefits and minimizing unwanted side effects depends on a clear understanding of the thermal and non-thermal biological effects of ultrasound as well as more accurate guidance of the ultrasound beam. This paper reviews the basic principles behind thermal and non-thermal (cavitation) biological effects of ultrasound, as well as general information and safety considerations for a wide range of therapeutic ultrasound methods either under study or in clinical use.

Keywords: Ultrasound; Therapeutic applications; Thermal effect; Non-thermal effect; Cavitation

Introduction

Ultrasound can be employed in many therapeutically beneficial applications. In therapeutic ultrasound procedures, energy is deposited in tissue to bring about different biological effects for therapeutic benefit [1, 2]. The very first large-scale use of ultrasound for therapeutic benefit was in the 1930s [3,4]; during World War II, people realized that the high-intensity ultrasound waves used to navigate submarines were heating and killing fish and the first therapeutic ultrasound mechanism of tissue heating and healing was envisioned [5]. This led to research using a focused ultrasound beam as an alternative to ablative procedures. As early as the 1940s, researchers tried to focus the ultrasound beam, strengthen the mechanism of heating at the focal point, and ablate tissue [6-9]. In the ensuing decades, the application of ultrasound for destruction of tissue in the brain for Parkinson's disease treatment and of the vestibular nerve for Meniere's disease treatment was explored [10,11]. The use of ultrasound was also established by the 1970s in physiotherapy because of its ability to speed up the healing process (by giving rise to blood flow in the treated area), decrease pain, and gently massage muscles, tendons, and ligaments; research also continued into further applications related to neurosurgery [12] and cancer treatment [13]. In the 1980s, the use of ultrasound in high-pressure amplitude shockwaves for mechanical destruction of calculi such as kidney stones and gallstones into fragments small enough to be passed from the body (lithotripsy) came

into use and replaced surgery [3]. In the last two decades, advances in the fields of imaging, physics, and engineering have expanded ultrasound use to various applications in medicine, including dentistry (for dental cleaning and disinfection) [14], cataract treatment (for ultrasound phacoemulsification cataract surgery) [15], acoustic targeted drug delivery (for delivering drug to different tissues) [16], lipectomy (for internal and external ultrasound-assisted liposuction) [17-19], and high-intensity focused ultrasound (HIFU) and magnetic resonance guided focused ultrasound (MRgFUS) treatment (for non-invasive ablation of soft tissue in the area of cancer therapy and surgery) [20-24]. The purpose of this review is to briefly outline the common and recent developed therapeutic applications of ultrasound, together with general information and safety considerations for a wide range of therapeutic ultrasound methods either under study or in clinical use. The basic principles behind thermal and non-thermal (cavitation) biological effects are discussed. This is followed by the description of a wide range of ultrasound treatment methods using heating, cavitation, or combined mechanisms of action. Prospective new therapeutic ultrasound methods are also presented.

Basic Principles of Ultrasound Tissue Interaction

Ultrasound can interact with biological tissues through heating as well as through non-thermal mechanisms, including acoustic cavitation, gas body activation, mechanical stress, or other unknown non-thermal processes

[25]. As the ultrasound beam travels through tissue, the amplitude of the original signal is attenuated due to absorption, reflection, or scattering at interfaces. When ultrasound passes through soft tissue, about 80% of the attenuation (energy loss) of the sound wave occurs through absorption. The amount of attenuation depends on the type of tissue. Table 1 shows the attenuation coefficient of different tissues, measured in decibels per centimeter at a frequency of 1 MHz. A higher attenuation coefficient means more energy loss; the highest attenuation coefficient is for bone, which means bone particularly limits beam transmission [26].

The attenuation coefficient is also directly affected by the applied frequency of the ultrasound wave and the distance the ultrasound wave travels in the body. Higher frequency waves are associated with higher attenuation and therefore limited penetration in tissue; in contrast, lower frequency waves have a lower tissue attenuation and therefore higher penetration depth [26]. For example, the attenuation of ultrasound waves by muscle, liver, and blood increases linearly with frequency, considering that muscle has a higher attenuation than liver, and liver has a higher attenuation than blood [26].

The frequency and intensity of ultrasound waves are determined based on the particular therapeutic application being considered and

Type of body tissue	Attenuation coefficient (dB/cm at 1 MHz)
Water	0.002
Blood	0.18
Fat	0.63
Liver	0.5-0.94
Kidney	1.0
Muscle	1.3-3.3
Bone	5.0

Table 1: Ultrasound attenuation coefficients of different body tissues at a frequency of 1 MHz [26]

the penetration distance into the body required to reach the target area. For example, in physical therapy applications ultrasound is applied at a relatively low frequency so as only to generate enough heat for pain relief and to speed healing in injured joints or muscle tissue. At frequencies of 1, 3, and 5 MHz, the ultrasound penetrates up to 4, 2, and 0.5 cm into the body and generates tissue temperatures of up to 40, 42, and 44 °C, respectively [27,28]. Different therapeutic applications of ultrasound and a comparison between ultrasound frequency, therapeutic outcome, and related bioeffect mechanism are given in Table 2 [29-45].

Ultrasound waves can distort and lead to a discontinuity or shock in the waveform as the pressure amplitude, the frequency, or the propagation length rises [3]. Decreasing frequency raises the probability of cavitation and gas body activation. Enhancing power or intensity tends to raise the probability and magnitude of all types of bioeffect mechanisms [3]. When ultrasound waves are transmitted into tissue, the acoustic pressures can become very large compared with the ambient pressure, with rare fractional pressure amplitudes of several megaPascals (MPa). This tensile stress is supported by the medium; for example, a diagnostic ultrasound scanner with a rarefactional pressure of 2MPa has a negative tension that is 20 times atmospheric pressure (i.e., 0.1 MPa) [3]. Fluid and tissue can withstand acoustic pressures greater than one atmosphere because of their cohesive molecular forces; however, their strength in this regard is limited. For longer times associated with ultrasonic frequencies at the lower end of the spectrum and at high acoustic pressures, the fluid may form small gas bubbles [46], a phenomenon termed cavitation (described in the next section).

Other biological effects of ultrasound can be considered the direct action of compressional, tensile, and shear stresses, and second-order phenomena include radiation pressure, forces on particles, and acoustic streaming [3]. Furthermore, secondary physical, biological, and physiological mechanisms such as vasoconstriction, ischemia, extravasation, reperfusion injury, and immune responses [47-49] can

Ultrasound Therapy Application	Therapeutic Outcome	Bioeffect Mechanism	Frequency	Reference
Physical therapy	Therapy of sports injuries, chronic inflammation, arthritis, and trauma	heating	1MHz	Newman [28]
Physical therapy	Bone fracture healing	unknown	1.5 MHz	Gebauer et al. [29]
Physical therapy	Treatment of the most superficial of tendon injuries	heating	3 MHz	Draper et al. [27]
Physical therapy	Skin & facial rejuvenation, fat removal, cellulite, scars & scar tissue, sunburn, bruises, superficial cuts & scrapes	heating	5 MHz	Newman [28]
Physical therapy	Bone growth stimulation	heating	1.5 MHz	Szaboo [30]
Hyperthermia	Cancer therapy	heating	1-3.4 MHz	Samulski et al. [31]
HIFU	Uterine fibroid ablation	thermal lesion	0.5-2 MHz	Tempany et al. [32]
HIFU	Glaucoma relief	thermal lesion	4.6 MHz	Burgess et al. [33]
HIFU	Laparoscopic tissue ablation	thermal lesion	4 MHz	Klingler et al. [34]
HIFU	Laparoscopic or open surgery	thermal lesion	3.8-6.4 MHz	Ninet et al. [35]
Focused ultrasound	Skin tissue tightening	thermal lesion	4.4-7.5 MHz	Alam et al. [36]
Extracorporeal lithotripsy	Kidney stone destruction	mechanical stress; cavitation	~150 kHz	Weizer et al. [37]
Intracorporeal lithotripsy	Kidney stone comminution	mechanical stress; cavitation	25 kHz	Lowe and Knudsen [38]
Extracorporeal shock wave therapy	Plantar fasciitis epicondylitis	unknown	~150 kHz	Haak et al. [39]
Phacoemulsification	Lens removal	vibration; cavitation	40 kHz	Packer et al. [40]
Ultrasound-assisted liposuction	Fat tissue removal	fat liquefaction; cavitation	20-30 kHz	Mann et al. [41]
Cutting tissue and scaling vessel	Laparoscopic or open surgery	thermal lesion and vibration	55.5 kHz	Koch et al. [42]
Intravascular ultrasound	Thrombus dissolution	gas body activation; not clear	2.2 MHz	Parikh et al. [43]
Skin permeabilization	Transdermal drug delivery	mechanical effect	55 kHz	Smith [44]
Focused ultrasound	Microbubble-aided gene delivery	cavitation	20 kHz-2 MHz	Porter and Xie [45]

Table 2: Different therapeutic applications of ultrasound and a comparison between ultrasound frequency, therapeutic outcome, and related bioeffect mechanism (thermal or non-thermal) (table design based on [3]).

cause further effects. Sometimes the impacts of these secondary effects are greater than the initial direct insult of ultrasound treatment [3]. The beneficial effects of therapeutic ultrasound include thermal and non-thermal effects. Thermal effects are due to the absorption of ultrasound energy, and non-thermal effects are due to cavitation, microstreaming, and acoustic streaming [1]. The ability to focus ultrasound waves enhances both thermal and non-thermal effects to a specific area of the body and has led to additional applications of focused ultrasound or high-intensity focused ultrasound for various therapeutic purposes. Thermal and non-thermal effects along with their related therapeutic applications are reviewed below.

Cavitation Effect

Cavitation is defined as the creation or motion of very small gas bubbles that are produced in tissue due to the alternating expansion and compression of tissue as an ultrasound wave propagates through it. These bubbles are produced in two fashions, either inertial and non-inertial (stable) cavitation [50]. Once the cavitation bubbles are produced, they may undergo nonlinear oscillations during many cycles of the acoustic wave, called “non-inertial cavitation”, or they may grow and collapse more or less violently, called “inertial cavitation” [51]. When low-pressure acoustic ultrasound is applied, non-inertial cavitation bubbles oscillate in size but do not collapse. This oscillating motion causes the rapid movement of fluid near the cavitation bubble that is called “microstreaming”. This micro-streaming can generate high shear forces that can lead to transient damage to cell membranes. This effect of non-inertial cavitation bubbles plays an important role in ultrasound-enhanced drug or gene delivery [52].

As opposed to non-inertial cavitation, inertial cavitation occurs due to violent oscillation, rapid bubble growth during the rarefaction cycle of the acoustic wave, and then violent collapse and destruction of the bubble. This collapse generates a very high pressure shock wave (20000-30000 bars) and high temperatures (2000-5000K) in the immediate microenvironment [50]. In addition, bubbles that collapse close to a cell wall or solid surface produce a very high-speed ($\sim 111 \text{ m/s}$) liquid jet that drives into the surface and results in pitting of the surface or cell wall [53].

This cavitation activity can be initiated in tissue when suitable cavitation nuclei are present or can be induced directly by pulsating pre-existing gas bodies, such as in the lung or intestine, or those introduced via ultrasound contrast agents. This causes local tissue injury (including cell death and hemorrhage of blood vessels) in the immediate vicinity of the cavitation activity [3].

Cavitation-based Applications of Ultrasound

Therapeutic applications of ultrasound based on cavitation include extracorporeal shock wave lithotripsy (ESWL), intracorporeal lithotripsy, and surgical ultrasonic instrumentation. The non-thermal effects of ultrasound in the human body are the basis for ESWL [37,54] for kidney stone destruction. The mechanism behind ESWL is that ultrasound waves focused over the kidney stone create shear waves that fracture the stone from within. The stone is shaved away from the outside through cavitation, resulting in cracks that are amplified by dynamic fatigue and further break the stone down [55]. To pulverize the stone to pieces less than 2 mm in size, which can pass naturally in urine, about 3000 ultrasound shock waves are triggered at a frequency of 2 Hz at the stone location [3]. Shockwaves have also been used for gall stone destruction, but this technique is not yet in widespread use [3]. Some other orthopedic applications for conditions such as plantar fasciitis and epicondylitis have a similar basis as lithotripsy and have been approved and marketed [39]. The biological side effects of lithotripsy affect virtually all patients [56]. The technique breaks blood vessel walls and leads to bleeding into the connective tissue and

interstitium. This can cause bruising of the parenchyma or formation of massive subcapsular hematomas [3]. Permanent loss of kidney mass then ensues as result of inflammation and scar formation [57]. In addition, the lithotripsy-induced injury causes systemic blood pressure increases, kidney function decreases, establishment of hypertension, and an increased rate of stone return, and also exacerbates the problem of stone disease [3,58]. Krambeck et al. [59] demonstrate a link between lithotripsy and diabetes mellitus. Furthermore, severe skin injury (second-degree skin burns) after ESWL have also been reported [60,61]. Such challenging clinical side effect can result from the generation of cavitation bubbles in the coupling gel (due to poor gel quality) or a lack of probe surface uniformity.

In intracorporeal lithotripsy, a rigid ultrasonic probe may be percutaneously manipulated and applied via the ureter for treatment of very large stones. In this technique, the stone is imaged by external ultrasound or fluoroscopy, or by ureteroscopy, endoscopy, or laparoscopy [3]. Hemorrhage, ureteral perforation, urinary tract trauma, and infection are considered risks of intracorporeal lithotripsy [3].

Although the benefits of lithotripsy to patients are many, the considerable risks require more investigations toward safer devices as well as optimization of the therapeutic ultrasound safety standards.

In biological research, frequencies as low as 20 to 90 kHz are applied to break up cells and tissues using a sonicator device [3]. Ultrasound-induced cavitation at low frequencies causes the break-up of cell walls and results in cell death. This is the basis behind ultrasound-assisted liposuction, a procedure in which excessive fat tissue is removed [41]; however, this procedure can result in bleeding, scarring, and infection [3].

Ultrasonic cavitation close to the probe tip can be used for very precise cutting in surgery. The ability of ultrasound to break up cells in the kHz frequency regime (e.g., a sonochemistry device), has found wide applications in biological research for destroying cells for extraction and other reasons. Ultrasound devices working in kHz frequency regimes are routinely used in clinical surgeries. Some advanced surgical procedures operating at frequencies of 20 to 90 kHz for tissue cutting, hemostasis, and tissue removal are routinely applied in clinics [3]. In ophthalmology, the lens of the eye is removed using an ultrasound probe working at kHz frequency during eye surgery for phacoemulsification for cataracts [40]. Another application of kHz-frequency ultrasound probes are as “harmonic scalpels” to rapidly stop bleeding by coagulating blood due to localized frictional heating [42].

Heating Effect of Ultrasound

Absorption of ultrasonic energy can lead to heating of tissues [3]. Ultrasonic-induced heating response *in vivo* is modified by the presence of bone, gas, and fluid. Sites in the body with higher absorption experience greater heating than surrounding tissues. For example, a calcified bone surface strongly absorbs ultrasound energy. Fetal bones absorb more energy compared to the surrounding fetal soft tissue, and the difference becomes greater as bone mineralization proceeds [46].

Ultrasound is usually generated from a piezoceramic crystal in very short cycle pulses (i.e., 1 to 5 cycle). Diagnostic ultrasound typically operates in the range of 2 to 12 MHz. Current diagnostic ultrasound equipment is unlikely to cause a temperature rise in tissue outside the normal physiological range [3]. Temperature elevation and potential bioeffects are kept negligible [62] by applying finite temporal average intensities and short exposure time principles [3]. However, hazardous temperature increases in tissue can occur during the use of physiotherapy ultrasound equipment. The heating caused by ultrasound is highly localized and limited to the region of the ultrasonic beam. It is possible to expose and so heat the whole of the uterus at the very early stages of a human pregnancy [46].

Heating-based Applications of Ultrasound

Heating is generated during therapeutic application of ultrasound either in the form of an unfocused beam with longer durations or focused ultrasound with a higher intensity than diagnostic ultrasound [3]. For example, in physical therapy the unfocused beam is utilized to treat tissues such as bone or tendon and enhance healing without injury; in contrast, a focused beam is utilized to concentrate the heat until tissue coagulates for purposes such as tissue ablation. Depending on the heat generated during ultrasound exposure, the effects can result from moderate heat, coagulative necrosis, tissue vaporization, or all three [3]. Therapeutic application of ultrasound based on heating can be subdivided into three categories: physical therapy, hyperthermia, and high intensity focused ultrasound.

Ultrasound for Physical Therapy

Physical therapists often use “therapeutic ultrasound”, which features an unfocused beam applied with coupling gel to warm tendons, muscles, and other tissues to treat conditions such as bursitis of the shoulder or tendonitis. This method of treatment uses sound waves to treat pain, inflammation, and muscle spasm. The purpose is to stimulate the tissue beneath the skin’s surface [63], improve blood flow, and accelerate healing [3]. Another application of ultrasound is sonophoresis or phonophoresis, in which ultrasound is used to assist transport of a compound into the skin [64]. As reported by Miller et al. [3], these techniques have a modest level of efficacy and patient benefit and a low level of risk. Ultrasound waves are applied to tissue by a round-headed transducer that can come in different shapes (Figure 1) to stimulate joints, ligaments, tendons, muscles, and other tissues. The gel is used on the skin to decrease friction and act as a conductor of the ultrasonic waves [63].

The ultrasonic waves pass through the skin and, through vibration and cavitation, cause deep local heating of tissues, soothe inflammation, and relieve pain. This heating increases blood flow, causes tissues to relax, and helps decrease local swelling and chronic inflammation. The increase in blood flow also delivers more oxygen and nutrients to the tissue, eliminates cell waste, and aids healing. Ultrasound can decrease the sensitivity and pain related to muscular trigger points. Physical therapy ultrasound can also be used to increase the delivery of applied drugs by enhancing the absorption of analgesics and anti-inflammatory agents to tissue through ultrasound waves.

Physical therapy ultrasound is conducted at low frequency ranges that depend on the deepness of the target area for treatment in the body. The ultrasonic frequency is the inverse of the ultrasound wavelength and its penetration in the body, meaning a lower frequency results in a larger wavelength and deeper penetration, and vice versa. The amount of energy released to the target area depends on the frequency, power, and absorption coefficient of the substance through which the sound waves travel. Table 3 [64-68] shows the typical frequencies used in physical therapy ultrasound units and related wavelengths, temperatures generated, and target organs.

Hyperthermia

Another heat-based application of ultrasound is hyperthermia (also called thermal therapy or thermotherapy), in which ultrasound is used to heat a relatively large amount of tissue to about 42°C for reducing tumor growth in cancer therapy [69]. In hyperthermia, multi-element applicators are used at a frequency range of 1 to 3.4 MHz [70,71]. Hyperthermia is almost always applied in conjunction with other cancer therapies, such as chemotherapy or radiation therapy [72,73]. Many clinical trials have focused on such combined applications and many have shown a considerable reduction in tumor size [72,73]. However, increased survival in patients was not always observed [73,74]. Research has shown that high temperatures damage and kill cancer cells. High temperatures damage proteins and structures within cells [75], cause less blood flow to the tumor by damaging blood vessels, and ultimately result in the death of cancer cells. However, the moderate heat produced in hyperthermia has not advanced to other clinical applications and has been replaced by high-intensity focused ultrasound [3].

High-intensity Focused Ultrasound

HIFU is one of the more active and developed research areas among all non-ionizing-energy methods, which include radiography, lasers, and microwaves [3]. The first application of HIFU was for thermal ablation of inoperable tissue related to Parkinson’s disease [10,76]. This non-invasive thermal ablation technique has been used for treatment of tumors in several organs and is on the verge of becoming an alternative to the standard treatment options of surgery, radiotherapy, gene therapy, and chemotherapy in future oncology practice. HIFU has been used for clinical treatment of different types of solid malignant tumors, such as those in the pancreas, liver, kidney, bone, pancreas, prostate, and breast,

Frequency	Ultrasound wavelength	Penetration depth into the skin	Temperature generated	Therapeutic outcome	Reference
1 MHz	1.6 mm	4 cm	40°C (104 °F)	Treatment of acute or chronic injuries and pain, bone injuries and arthritis treatment, nerve, muscle, tendon injuries and pain, arthritis, bursitis, wound care, exercise recovery; beauty-related applications	Newman et al. [28], Draper et al. [27], Enwemeka et al. [65], Ebenbichler et al. [66,67], Langford et al. [68]
3 MHz	0.53 mm	2 cm	42°C (106°F)	Treatment of superficial tendon injuries; beauty-related applications for facial treatments such as cheeks, forehead, chin	Draper et al. [27], Newman et al. [28], Langford et al. [68]
5 MHz	0.3 mm	0.5 cm	44°C (108°F)	Beauty-related applications for facial treatment such as eye area	Draper et al. [27], Newman et al. [28], Langford et al. [68]

Table 3: Typical frequencies used in physical therapy ultrasound units and their associated wavelengths, temperatures generated, and target organs.



Figure 1: The different shapes of physical therapy ultrasound transducers widely used in clinics.

as well as uterine fibroids and soft-tissue sarcomas. The HIFU technique has FDA approval for clinical use in the USA for the treatment of uterine fibroids [32], cardiac ablation [35], visceral soft tissue ablation [34], and aesthetic treatment to lift the eyebrow [36,77]. Other HIFU-based therapies are under study for clinical applications such as modulation of nerve conductance [78], benign prostate hyperplasia, and prostate cancer, but do not yet have FDA approval. HIFU has also been utilized in methods for curing glaucoma [33]. Other HIFU-based therapeutic techniques for the treatment of benign prostatic hyperplasia (BPH), prostate cancer [79,80], hepatic cancer, and pancreatic cancer are still under investigation.

The HIFU technique focuses the ultrasound beam in a small area and generates a tissue lesion typically a few mm in diameter and in length. The absorbed energy raises the tissue to a lethal temperature, with very sharp thermal gradients so that the boundaries of the volume under ablation are clearly confined without damaging the overlying tissues [81]. In a HIFU system, a signal generator connected to a focusing transducer generates very high local intensities (greater than 1 kW/cm² at the focal point) at frequencies ranging between 0.5 and 7 MHz [3]. In this method of treatment, the ultrasound beam is focused several millimetres to centimeters away from the transducer plane. In order to determine the location of the treatment zone and also monitor tissue changes in the target area, two image guidance and treatment monitoring methods are applied: magnetic resonance imaging (MRI) and ultrasound imaging. The related treatment techniques are called magnetic resonance guided focused ultrasound (MRgFUS) and ultrasound guided focused ultrasound (USgFUS), respectively. USgFUS systems incorporate both treatment and imaging modalities in one system. The ultrasound-based monitoring in HIFU treatment is based on a combination of sound velocity, attenuation, stiffness, and vapor content variation in the target area [82]. HIFU guided by ultrasound has limited target definition and monitoring capability of the ablation process. MRgFUS provides more accurate targeting and real-time temperature monitoring. MRgFUS surgery is a non-invasive thermal ablation technique in which MRI is used for target definition, treatment planning, and closed-loop control of energy deposition. In fact, MRgFUS as a therapy system allows targeting, localizing, and monitoring in real time without damaging normal structures. This precision has made MRgFUS an attractive method for surgical resection or radiation therapy of benign and incurable tumors. MRgFUS has been approved for treatment of uterine fibroids, and is undergoing clinical trials for the treatment of breast [83,84], liver [85,86], prostate [87-89], and brain cancer [90,91] as well as to relieve and lessen pain in bone metastasis [92-94]. Because MRI is capable of providing the temperature variation within the treatment zone [95], generating detailed images of soft tissues in the body, discovering a wide spectrum of space-occupying soft-tissue lesions, and creating real-time images and thermographic guidance during the procedure, MRgFUS has become a novel and non-invasive method of treatment. MRgFUS plays an important role in the development of neuro therapeutics and brain-based disorders and has been proposed as an alternative to open neurosurgical procedures for a wide variety of indications. Specialized MRgFUS systems have ultrasound therapy sub-systems integrated into MR-imagers. Such systems are employed in the treatment of uterine fibroids [32], breast cancer [96], and prostate cancer [97].

All of the above HIFU techniques are applied by external devices; however, natural orifices are also employed, such as in transrectal treatment of prostate cancer [98] and endoscopy via an intraductal probe for bile duct tumors [99].

Non-invasive aesthetic applications of HIFU will provide a safer alternative to liposuction for cosmetic applications [100]. The exposure of superficial tissue to HIFU leads to a contraction of the dermis or to demolition of fatty tissue [77,101]. In this technique, both thermal as well as non-thermal mechanisms of ultrasound are involved.

HIFU has also been utilized to treat a trial fibrillation by tissue ablation to achieve pulmonary vein isolation [3].

During HIFU applications, undesired tissue injury, unwanted burns, and pain can occur as significant ultrasound energy is delivered to a localized area of tissue [3]. In addition, HIFU can cause vasospasm and hemorrhaging when concomitant cavitation is also generated in the tissue [102], impotence and incontinence during prostate cancer treatment [103], or creation of an a trial-esophageal fistula during a trial fibrillation treatment [104]. Furthermore, fistula formation and rib necrosis with delayed rib fracture [105] are also considered to be serious complications that can occur following hepatic and pancreatic cancer treatment [3].

Therapeutic Applications of Ultrasound Based on Combined Mechanisms

Other therapeutic techniques involve multiple mechanisms of ultrasound.

In intravascular catheters, a MHz-frequency transducer is placed near the tip for increasing dissolution of thrombi [43]. When the catheter is placed into a deep vein thrombus, the ultrasound is targeted radially into the thrombus or an infusion of a thrombolytic drug, such as tissue plasminogen activator, is delivered into the thrombus [3]. Ultrasound-assisted drug delivery significantly decreases treatment time by increasing the permeability of cell walls and the infusion of drugs into cells.

Another application of ultrasound is skin permeabilization, which may replace multiple use of needles for drug delivery through the skin for medicines such as heparin and insulin [44]. Drug diffusion through the stratum corneum is difficult for molecules with a molecular weight greater than 500 Da [106]. Using low-frequency ultrasound (<100 kHz), the permeability of the stratum corneum (which is considered a protein diffusion barrier) increases [107] and the drug can pass and reach the inner layers and finally the capillary vessels where it is absorbed [108].

The use of low-intensity pulsed ultrasound (about 1.5 MHz) for accelerating the healing of bone fractures for cases such as non-union and non-healing fractures is another therapeutic action of ultrasound [3]. The biophysical mechanism behind this therapeutic action is not yet clear.

New Research Areas for Therapeutic Applications of Ultrasound

Several streams of research are investigating other therapeutic applications of ultrasound. These new methods mostly rely on low frequency and power ultrasound aided by microbubbles or very high power ultrasound for the production of vigorous cavitation [3].

The application of low-frequency ultrasound for direct sonothrombolysis for treatment of thrombotic disease such as stroke is a new strategy [109]. However, this method showed increased brain hemorrhage in a clinical trial [110]. Microbubbles play an important role in increasing thrombolysis and improving stroke therapy [111].

Another potential use of ultrasound is to produce cortical and hippocampal stimulation in mice [112]. Non-thermal mechanisms have been hypothesized to be responsible for the neuronal effects in this method, as the temperature gradients were very small (<0.01°C) [3].

Ultrasound-aided drug delivery is another area of study. This technique is based on microbubbles and is under study for direct and targeted therapies that release drugs at a specific location within the body (such as a cancerous area) without affecting the rest of the body. It can also be used to force drug flow from a vessel out into the surrounding tissue and to increase intracellular delivery [3]. The advantage of ultrasound

microbubble techniques over other techniques such as nanoparticle or liposome delivery systems is the capacity for external control [3]. DNA transfer in gene therapy applications has also been under extensive study [113].

Histotripsy, equivalent to lithotripsy but at a higher frequency and with very high amplitude pulses, uses only the cavitation mechanism for tissue ablation [114] to homogenize targeted tissue, such as tumors, with little heating [115].

Summary

Both thermal and non-thermal (cavitation) effects play very important roles in all therapeutic applications of ultrasound. These effects can be hazardous biologically, and are therefore avoided in diagnostic applications of ultrasound but used in therapeutic applications of ultrasound. The application of ultrasound at high levels of exposure has well-recognized adverse biological effects, which are harnessed for therapeutic purposes in most therapeutic devices. The use of therapy ultrasound devices comes with the risk of affecting healthy organs and causing substantial bioeffects. The benefits and potential risks associated with each therapeutic device should be considered and explained to patients. For example, non-invasive lithotripsy has tremendous benefits compared to conventional surgical treatment even though it has an increased risk of hemorrhage and longer-term kidney injury.

Although measures and guidelines are in place to avoid unwanted bioeffects and deliberate caution on the part of the operator of the device can help decrease the risk of injury, safe and accurate use of ultrasound devices is essential to minimize the risks.

The cavitation mechanism that is exploited to ablate tissue, disrupt cells, destroy kidney and bladder stones, and treat thrombolysis, among many other applications, is secondary to the ultrasound exposure. Microbubble-based therapeutic strategies are still under investigation for direct and targeted therapeutic purposes. The problems of dosimetry and control of cavitation and microbubbles are challenging. Researchers studying cavitation are endeavoring to understand medium and cavitation nuclei, the ultrasound field, and when cavitation occurs [3]. Understanding the connection between the cavitation threshold and the medium and cavitation nuclei is desired and understanding the ultrasound field requires accurate measurement of the ultrasound beam area. Knowing when cavitation occurs requires the direct observation or indirect monitoring of cavitation events. Different detection techniques can quantify an ultrasound field [116,117] and measure cavitation through the noise of bubble collapse [118]. However, considering the rapid development of therapeutic ultrasound techniques that mostly work based on cavitation and microbubbles, the emergence of more accurate and new cavitation detection methods is essential to monitor and control cavitation for optimum patient safety. Repeating treatments can serve to accumulate unwanted bioeffects and damage already compromised organs (e.g., the kidney in lithotripsy) and lead to permanent loss of organ function. Therefore, defining the cumulative dose and anticipating the level of bioeffects after each treatment is also required.

Therapeutic applications of ultrasound directly depend on the interaction of the sound field with the tissue to induce the desired beneficial bioeffect. The exposure parameters used for ultrasound therapies are often noticeably different. This requires sufficient knowledge of acoustic mechanisms with respect to the interaction of ultrasound with tissue to improve the safety of ultrasound use and to facilitate the design of new therapeutic applications of biomedical ultrasound. Safety improvements in therapeutic ultrasound devices need to be pursued and more research should be dedicated to this issue. Exposimetry, dosimetry, and accurate and precise evaluation of acoustic fields in water and *in situ* should be

done carefully and followed by animal studies to identify possible harmful bioeffects in humans. New accurate and more effective means of detection and monitoring of acoustic cavitation should be in place to continually regulate the acoustic output levels of therapeutic and diagnostic devices for their safe operation.

Abbreviations

BPH: benign prostatic hyperplasia; **ESWL:** extracorporeal shock wave lithotripsy; **HIFU:** high-intensity focused ultrasound; **MPa:** megapascals; **MRgFUS:** magnetic resonance guided focused ultrasound; **MRI:** magnetic resonance imaging; **USgFUS:** ultrasound guided focused ultrasound.

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