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Perspectives in clinical uses of high-intensity focused ultrasound ☆

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Abstract

Focused ultrasound holds promise in a large number of therapeutic applications. It has long been known that high intensity focused ultrasound can kill tissue through coagulative necrosis. However, it is only in recent years that practical clinical applications are becoming possible, with the development of high power ultrasound phased arrays and noninvasive monitoring methods. These technologies, combined with more sophisticated treatment planning methods allow noninvasive focusing in areas such as the brain, that were once thought to be unreachable. Meanwhile, exciting investigations are underway in microbubble-enhanced heating which could significantly reduce treatment times. These developments have promoted an increase in the number of potential applications by providing valuable new tools for medical research. This paper provides an overview of the scientific and engineering advances that are allowing the growth in clinical focused ultrasound applications. It also discusses some of these prospective applications, including the treatment of brain disorders and targeted drug delivery.

1. Introduction

The concept of replacing a surgeon's scalpel with a noninvasive procedure has attracted attention in medicine for more than half a century. Ultrasound has become a leading method for realizing such procedures, due to its ability to accurately focus energy into the body in order to heat and destroy small volumes of tissue. A wide range of treatments have been investigated to treat tumors, to ablate the prostate for benign hyperplasia (BHP) [1–3], to control bleeding [4], for cardiac treatments [5], to treat various eye conditions [6], and to treat brain disorders [7]. An increasing number of clinical treatments and trials are being conducted worldwide for tumor ablation in various organs, while exciting prospects for enhancing and expanding present therapies are underway.

The idea of using ultrasound for medical treatment is not new. In fact, it predates its suggested use as a diagnostic tool. High intensity focused ultrasound for ablating tissue dates back more than 60 years. However, early treatments returned variable results due to the inability to monitor and control treatments. It is primarily new developments in targeting and monitoring over the past decade that have made many previously suggested procedures now reliable and practical. Near-real-time noninvasive monitoring has permitted quality assurance and improved treatment targeting, monitoring, and evaluation. Concurrently, significant advancements have occurred in high power ultrasound transducer array designs, materials, and driving systems. The combined imaging and driving technologies have allowed greatly increased beam control, resulting in reduced treatment times and the ability to correct distorted beams [8,9].

As technological advancements improve the ability to control energy deposition, there is an increasing concerted effort toward understanding the biological interactions and consequences of focused ultrasound. Ablation of tissue by coagulative necrosis—achieved by raising its temperature above approximately 60 °C—is the most understood mechanism of cell death. However, numeric and experimental studies are examining improved and faster treatments by promoting cavitation-enhanced damage. Methods are being investigated that induce cavitation with short, high amplitude pulses, as well as with the introduction of microbubbles into the bloodstream. Beyond thermal ablation, biological responses to ultrasound offer the exciting prospect of greatly expanding the use of focused ultrasound to include targeted drug delivery and certain therapies. Examples of such responses include increased gene

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transfection rates, the induction of cell apoptosis, and the opening of the blood brain barrier (BBB) [10,11].

This paper highlights several prospective procedures that could potentially result in widespread clinical use in coming years. It does not attempt to provide a comprehensive overview of high intensity focused ultrasound, but rather it focuses on a few promising areas. Moreover, it is noted that a number of other interesting therapeutic ultrasound applications are being investigated which do not use "high intensity" or "focused" beams, and thus are neglected here. For a concise historical overview of the subject, the reader may refer to a number of well-written reviews on the subject [12–14] which cover both historical and contemporary uses.

2. Targeting and monitoring

In principle, the technology of focusing ultrasound into tissue to induce temperatures high enough to kill cells is straightforward (see Fig. 1). It can be achieved with a single, spherically-curved radiator operating at frequencies approximately between 0.5 and 10 MHz, with most procedures performed around 1.5 MHz. The intensity achieved at the focus varies with the procedure in the range of 10^3–10^4 W/cm^2, sustained for 1–30 s. The primary criterion is that the frequency be high enough to allow significant energy absorption at the focus, yet not so high as to cause appreciable energy loss in the region between the transducer and the focus. Unfortunately, tissue inhomogeneities can distort the intended focal point as well as make the actual temperature rise at the focal point very hard to predict. Thus, to provide insight on the behavior of the therapeutic ultrasound field, it has been necessary to introduce noninvasive monitoring methods.

Inability to predict actual temperatures makes quantification through noninvasive targeting and monitoring particularly important. If a small "exploratory" temperature rise can be measured at the focus immediately before treatment it (1) provides assurance and (2) may be used to better plan the actual damage that will occur when ultrasound is applied at therapeutic levels. Ultrasound, CT, and magnetic resonance imaging (MRI) have all been used for guiding ultrasound exposures. Each of these modalities potentially offers the ability to detect the time-dependent temperature elevation [15–18]. However, to date only MRI has been shown to accurately record focal temperature rises in vivo.

A number of groups have been developing ultrasound surgery systems that use MRI to map temperature elevation online during the therapy sonications [19–24]. This method is now under clinical use in the treatment of breast tumors, and the treatment of uterine fibroids [25], which [26,27] is presently in the process of becoming a clinically accepted procedure in a number of countries. MRI has been shown to effectively use temperature information to determine damage parameters [28]. Improved detection is expected with present research in the area of motion detection. Such monitoring and detection will almost certainly play an increased role in complicated treatment areas such as the brain. Early clinical experience is very encouraging. However, the technique is somewhat limited by the MR-compatible ultrasound equipment required for performing the procedures and the relatively high cost of MRI. It is likely that focused ultrasound therapies would benefit a larger number of patients if cheaper targeting and monitoring methods were available.

An alternative to MRI for treatment monitoring is diagnostic ultrasound. Ultrasound guidance offers the potential of lower cost and compact focused ultrasound devices, which could potentially be used in outpatient settings, and could significantly reduce costs, allowing focused ultrasound to have a greater clinical impact worldwide. Unfortunately, controlled lesion formations are difficult to detect with commercial scanners.

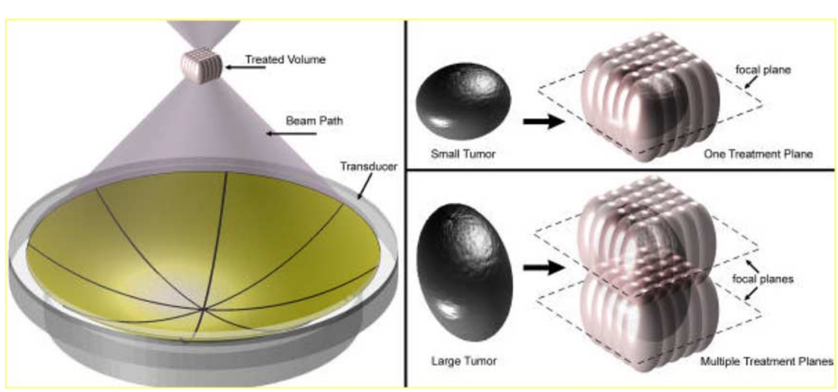

Fig. 1. A high intensity focused ultrasound transducer (left). Tumors (right) are treated by successive ultrasound application, either by mechanical movement of the transducer, or by electronic steering of a phased transducer array (graphic courtesy of N. McDannold).

A number of methods have been studied for lesion detection using changes in tissue attenuation [29], elastography, ultrasound-stimulated acoustic emission (USAE) [30], and radiation force measurement [31]. Certain methods, such as elastography may have application both for tumor detection and for treatment evaluation. Souchon et al. [32] applied lesion detection in vivo, but additionally indicated the intermittent ability to detect tumors in preoperative images.

Another central role of diagnostics is in monitoring of the actual treatment, filling the middle stage between targeting and evaluation. For treatment monitoring, ultrasound imagers can detect gas induced by cavitation or evaporation. A real-time method has been developed that detects the interference between the HIFU beam and the imaging beam [33]. These ultrasound methods may provide a role in assuring proper treatment. However, the major drawback of ultrasound has been the lack of a clinically viable method for quantifying the temperature rises in the treatment region.

Potential ultrasound approaches to temperature monitoring are based on thermally induced changed to tissue properties. These properties include change in sound speed, attenuation, reflection coefficient, and stiffness. As indicated by Miller et al. [34] in a numeric investigation, there are limits on when such imaging is possible. In their study, they examined the minimum ultrasonic signal necessary for visualizing a heated region in liver. They found that the threshold SNR for detection was at least 20 dB, and that for liver containing a moderate level of fat, the heated region could not be visualized altogether. Alternative imaging approaches such as transmission imaging methods are being examined as a possible temperature sensor, given adequate information of the thermal behaviors of the relevant tissue [35,36]. An example of transmission thermal imaging of a focused ultrasound beam is shown in Fig. 2. Research led by ter Haar has considered the use of reflex transmission imaging, while our group is presently investigating a phase contrast transmission approach. Another suggested approach uses elastographic measurements to detect changes in travel time [37], and the use of ultrasound stimulated acoustic emission (USAE) has also been studied. Recently, it was indicated that the frequency shift of the resonant peaks of a USAE signal is temperature dependent, and may have application for therapeutic monitoring [30]. The ability to detect temperature elevations on the order of several degrees would greatly increase the attractiveness of diagnostic ultrasound. It would not only allow the focused beam to be accurately positioned, but additionally it would allow damage to be predicted using methods only available now with MRI.

3. Improved ultrasound delivery

3.1. Bubbles and cavitation

The primary mechanism for destroying tissue with focused ultrasound is coagulative necrosis by thermal absorption. Generally, this is attempted as a controlled energy transfer, where temperature rises are assumed linearly proportional to the acoustic field intensity. Cavitation-induced damage (thermal or mechanical) is a second mechanism, but has generally been avoided due to variable intensity values and unpredictable lesion shapes. In fact, the damage potential from cavitating bubbles is so great that understanding and quantifying their effects in vivo has been a central topic of focused ultrasound research. Holt et al. [38] provide an excellent brief overview of the topic in the context of high intensity focused ultrasound. Recent experimental studies have been investigating the idea of promoting cavitation for enhancing the level of ablation and reducing required exposure times. This is in contrast to previous approaches, where cavitation was viewed as an unpredictable damage mechanism that should be avoided.

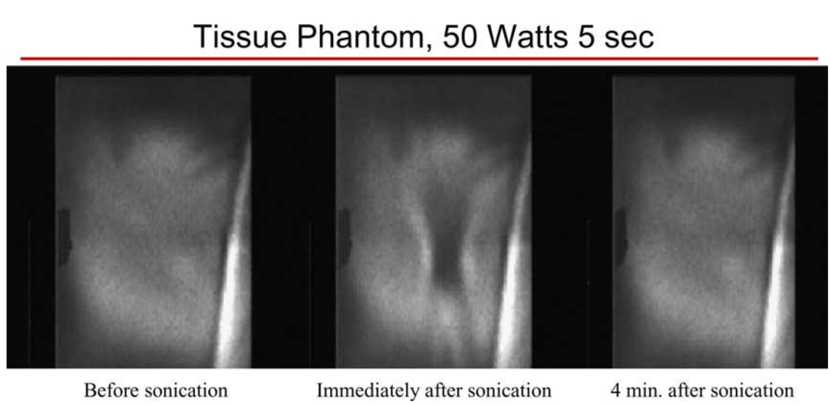

Fig. 2. Temperature-dependent transmission ultrasound images taken before (left), immediately after (center), and 4 min after heating with a focused transducer. The axis of propagation is from bottom to top of the image.

Sokka et al. [39] have proposed a focused ultrasound surgery protocol that induces and then uses gas bubbles at the focus to enhance the ultrasound absorption and ultimately create larger lesions in vivo. A recent study by Hynynen et al. [40] showed that the US exposure levels currently used for blood flow measurements in brain are below the threshold of blood-brain barrier opening or brain tissue damage. However, the same study indicated that damage can be induced if the exposure level is increased. This brings the interesting prospect of using contrast agents to induce damage at relatively low time-averaged ultrasound powers. If a controlled procedure can be developed, it could feasibly eliminate any problems that occur with near-field heating.

3.2. Improved modeling and prediction

The complexity of human tissue structure and its response to stimulus makes modeling of ultrasound in the body a daunting task. Despite a large body of empirical data, ultrasound energy deposition is still relatively poorly understood. To better understand ultrasound the large number of interactions that take place in tissues, and to ultimately improve the predicted effect of ultrasound in the body, studies continue to examine higher-order propagation effects, such as the work by Filonenko and Khokhlova [41], and cavitation effects in tissue [42]. Many models have been expanded to include, for example, the interaction of sound with microbubbles and the role of perfusion and blood vessels.

Modeling is also now playing an important role in reconstructing distortions caused by tissue inhomogenities. A barrier to focused ultrasound treatments has been the presence of bone or strong tissue variation in the beampath. To overcome these aberrations, algorithms can reconstruct a given focus using information obtained a priori to predict the beampath, and then compensate for the expected phase and amplitude changes using phased transducer arrays. Fink and coworkers [43] have investigated combining time-reversed acoustics with a finite difference model for adaptive focusing. Alternatively, a layered-projection model has been used to focus through the skull [44]. This approach applies the forward and backward planar projection methods [45] to the problem of propagating acoustic energy through bone. The method has the advantage of being computationally efficient and is adaptable to other areas in the body for propagating an arbitrary focused wave through any number of arbitrarily oriented layers. Such algorithms will be vital to future transskull applications in the brain. They also may allow correction through fat layers as well as application of focused ultrasound through the rib cage [46].

3.3. Phased array technologies

Phased arrays have multiple uses in high intensity focused ultrasound. The most recognized use is for steering the ultrasound focus. However, arrays can also produce multiple simultaneous foci for shortened treatment times. They can also be used to restore a distorted focus with aberration correction. High power applications have required the development of new array designs as well as high power driving systems. The use of 1–3 PZT composite materials has become a popular alternative to individual PZT elements [47]. These arrays offer the ability to output high acoustic powers over a higher bandwidth than high-Q solid PZT transducers. Concurrently array designs for specific applications have been improved through theoretical optimization and performance evaluations. For example, Tan et al. [48] studied maximum steering performance under the constraints of transrectal applicators. Transducers with at least 500 elements have been constructed for high-power focused applications. A number of groups and companies have developed phased array driving systems designed specifically for high power ultrasound arrays. For example, MR-guided therapies have prompted the development of an assortment of MR-compatible transducers. An interesting new development is underway by the group headed by M. Fink at the University of Paris and ESPCI. This group has been developing a system that tracks tumor motion in real-time, and then automatically performs a three-dimensional correction of the therapy beam.

4. Developing uses for high intensity focused ultrasound

A relatively large body of clinical experience in high intensity focused ultrasound has been achieved in the treatment of the prostate. New methods continue to be developed for both localized prostate cancer [49] as well as BHP. However, both ultrasound-guided and MR-guided clinical trials are occurring for the treatment of a number of organs. An ultrasound-guided system developed in China (HIAFU Technology Co. Ltd., Chongquing) has treated a sizable number of liver patients and other tumors in China and is now being studied for the treatment of liver tumors and kidney tumors at Oxford University. Other promising and rapidly growing uses of MR-based therapies are in the breast [50,51], and in the treatment of uterine fibroids [26,27], as discussed above.

Focused ultrasound may have other roles in treatments when used to occlude blood vessels, or when used with antitumor agents or other drugs that can be activated using ultrasound. Ultrasound can significantly enhance transgene expression in cells. It has been reported that tumors have been significantly sensitized to the antitumor effect of certain complexes, such as Ga-porphyrin [52,53]. It has been established that focused ultrasound can be used to affect the vascular structure, such as reproducible vascular occlusion in vivo [54]. In one study, histologic examinations of ultrasound targeted tumor cells [55] showed that treated tumor cells indicated not only coagulative necrosis, but also that small tumor vessels were severely damaged by the HIFU treatment. The results indicate that damaged tumor vessels may play an important role in tumor cell death. Apoptosis, has also been observed in histolological examinations after sonications [56], suggesting the possibility of noninvasive localized programmed cell death. Finally, there is a large area of study in the area of enhanced gene transfection rates under ultrasound, including a recent study on the control of transgene expression in vivo using a thermally-sensitive promoter and MRI-guided focused ultrasound [57].

4.1. Noninvasive brain therapies

Perhaps the most exciting future for HIFU ultrasound is its use in treating brain disorders. In the 1950s Fry et al. [58] produced lesions in the central nervous system with focused ultrasound. However, in these early ultrasonic operations in brain, a soft tissue window was required, as skull bone was considered impenetrable. A number of recent studies propose the use of large area ultrasound arrays [59] to overcome distortion caused by the skull (Fig. 3). The primary goal has been to create an array and focusing method that can focus ultrasound into a precise location in the brain and destroy the tissue at the focus, while still preserving the areas around it. A technique for completely noninvasive focusing ultrasound through the human skull has been described and verified using an ensemble of 10 human skulls [44] using a 320-element array. The approach is based on a layered wavevector-frequency domain model, which propagates ultrasound from a hemisphere-shaped transducer through the skull using input from CT scans of the head [60]. An adaptive focusing technique [43] has been demonstrated, which also relies on CT information as input to a finite difference model.

The ability to focus into the brain may have implications that go far beyond tumor treatment. Brain research has demonstrated that focused ultrasound can selectively open the brain's blood-brain barrier (BBB) [61]. More importantly, recent studies indicate that controlled, monitored opening of the BBB can be consistently opened with focused ultrasound exposures in the presence of ultrasound alone [11] and with the introduction of a contrast agent [10].

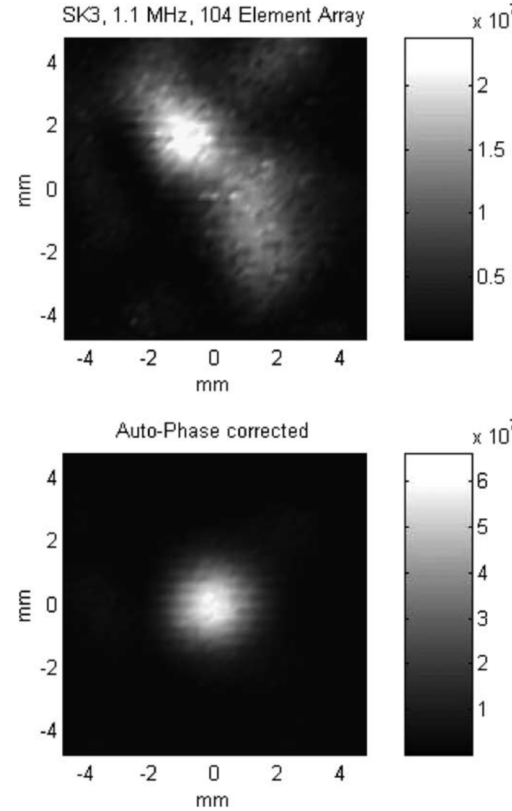

Fig. 3. A demonstration of transskull focusing. Scanned hydrophone image (mVpp^2) of an ultrasound field directed through a human skull bone. Scans were performed before (above) and after (below) transducer phase correction.

5. Summary

An increasing body of literature has appeared worldwide on new and prospective clinical uses of high intensity focused ultrasound. This is in part due to technological advances that are now allowing long-proposed procedures, and in part due to increased physical and biological understanding of the bioeffects of focused ultrasound. Evidence of increased interest in the field is reflected in the creation of the International Society on Therapeutic Ultrasound in 2001 (www.istus.org), which holds an annual symposium, and the establishment of the International Society of Magnetic Resonance in Medicine's Workshop on MRI-Guided Focused Ultrasound Surgery, held in June, 2001 (www.ismrm.org/workshops/ultrasound).

In the short term, the primary use of high intensity focused ultrasound in medicine will be for tumor ablation. These applications are expected to see expanded use worldwide, particularly in treating uterine fibroids. As more ablation techniques expand into the clinic, some exciting improvements and new uses lie on the horizon, including use for targeted drug delivery and gene therapies. Finally, focused ultrasound could potentially provide considerable benefit to the treatment of a wide range of brain disorders if opening of the BBB can be demonstrated as safe and effective in humans.

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