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Emerging Non-Cancer Applications of Therapeutic Ultrasound

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Abstract

Ultrasound therapy has been investigated for over half a century. Ultrasound can act on tissue through a variety of mechanisms, including thermal, shockwave and cavitation mechanisms, and through these can elicit different responses. Ultrasound therapy can provide a non-invasive or minimally invasive treatment option, and ultrasound technology has advanced to the point where devices can be developed to investigate a wide range of applications. This review focuses on non-cancer, clinical applications of therapeutic ultrasound, with an emphasis on treatments that have recently reached clinical investigations, and preclinical research programs that have great potential to impact patient care.

Introduction

There is an increasing trend towards the development of minimally invasive or non-invasive medical interventions. The motivation for this is obvious since these treatments result in shortened hospital stays and recovery times, minimal damage to surrounding healthy tissues and a reduced risk of infection. The therapeutic potential of ultrasound (US) has long been recognized, and it has become well established in physiotherapy applications [1], including fracture healing [2], and for specific applications such as lithotripsy for the dissolution of kidney stones [3]. However, many of the applications identified in early studies failed to advance into wider-spread use for a number of reasons including limitations of the existing ultrasound methods and competing technologies. For example, during the 1950's the Fry brothers treated over 100 patients for various neurological disorders using focused ultrasound (FUS) [4]. However, until the late 1990's it was considered impossible to focus ultrasound through the skull bone [5]. The need to create a skull window to apply the ultrasound prevented ultrasound brain treatments from being adopted in favor of existing techniques such as open surgery or deep brain stimulation. However, advances in ultrasound techniques have overcome many of the early limitations, rekindling interest in previously abandoned applications and fueling the discovery of new ones.

There is a large body of work dedicated to the use of ultrasound for treating cancer, and several reviews exist on the topic [6, 7]. There are also a growing number of non-cancer

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applications of therapeutic ultrasound. This review examines emerging applications of ultrasound for treatments of diseases and disorders other than cancer. Both treatments that are currently being investigated in humans and promising pre-clinical studies demonstrating novel applications will be reviewed.

Mechanisms of Action

Ultrasound elicits a therapeutic effect through one of several mechanisms. The therapies discussed in this article can be broadly grouped into three categories (Fig.1), thermal therapies, shockwave therapies and cavitation mediated therapies, based on the dominant acting mechanism. Therapies may also be based on a combination of these. For example, thermal therapies may also use cavitation to enhance heating [8].

Thermal therapies can be of two types, hyperthermia or ablation. In hyperthermia longer ultrasound exposures are used to raise the temperature by a modest amount and maintain it for several minutes. Hyperthermia has been used as an adjuvant to radiation therapy [9] and for the release of drugs from thermally activated carriers [10]. Conversely, in ablation short, higher power sonications are employed to induce a sharp temperature rise and rapidly necrose tissue.

Shockwave therapy uses very high pressure and short pulses to deliver a shockwave at the target. Shockwave therapy is well established for dissolution of stones [3] and is also widely used in physiotherapy [11]. A shock produces a high stress on the tissue at the focus and generates inertial cavitation [12, 13].

Finally, cavitation-mediated therapies may make use of either stable or inertial cavitation, or both. Both stable and inertial cavitation enhance the therapeutic effects of ultrasound. However, in inertial cavitation the gas or vapor body collapses, which produces extreme local temperatures and pressures. So while stable cavitation can induce bioeffects without permanent tissue changes, inertial cavitation is generally associated with at least some level of irreversible damage.

All three of these types of treatment are being investigated for clinical uses. In Figure 2, an illustration is shown highlighting some of the applications of therapeutic ultrasound. In the following sections specific applications of thermal, shockwave and cavitation-mediated treatments for different treatment targets (abdomen, cardiac, brain, extremities, cosmetic) are reviewed.

Abdominal

The most established new application of therapeutic ultrasound in the abdomen is for the treatment of uterine leiomyomas, or fibroids. Uterine fibroids are benign tumors that are diagnosed in approximately 25% of women [14]. Fibroids often occur in women of reproductive age and the only complete cure for symptomatic uterine fibroids is radical hysterectomy, which is invasive and does not allow future pregnancies [14]. Alternatives to hysterectomy exist, but are invasive, ineffective or do not preserve reproductive capabilities. Focused ultrasound ablation of uterine fibroids in patients was first reported by Tempany et

al., [15], and regulatory approved MRI-guided devices for this procedure exist (Exablate2000, InSightec Inc [CE-mark, FDA]; Sonalleve, Phillips [CE-mark]), which have been used to treat thousands of women over the past decade. Using MR-thermometry, the temperature rise induced at the focus can be mapped to ensure that target temperatures (60–70°C) are achieved [15, 16, 17].

As a benign tumor, fibroids are an excellent target for MR-guided focused ultrasound since even partial volume ablation results in a reduction in pain and an improvement in symptom severity score [18]. While early studies were restricted to treating only 50% of the total volume due to safety concerns, recent studies ablating larger volumes have been performed without significant increase in the number of adverse effects [19]. Based on retrospective studies, pregnancy following focused ultrasound ablation of uterine fibroids appears to be safe [20]. The symptom relief has also been found to be lasting, with one study reporting 88% of patients with improved symptom relief at 12-months following treatment [21]. One approach in treating uterine fibroids is to target the supplying vessels [22], which may be particularly useful in highly vascularized fibroids where perfusion limits the achievable temperature elevation.

A recent study examining the cost effectiveness of different treatments for uterine fibroids found MR-guided FUS to be more cost-effective than uterine artery embolization or hysterectomy [23]. However, not all women are eligible for MR-guided FUS, either because of clinical contraindications or because of anatomical limitations, such as fibroid volume or the presence of the bowel in the acoustic beam path [24, 25]. Further, access to the technology remains largely limited to major centers.

Another interesting application of ultrasound in the abdomen is for acoustic hemostasis, the use of ultrasound to control active bleeding. Using HIFU to coagulate tissue, it has been shown in pre-clincal models that liver [26], splenic [27] and gastrointestinal (GI) bleeding [28] can be controlled, and thus there is great potential to use this technique to treat traumatic injuries. Although earlier studies relied on thermal mechanisms to induce hemostasis, hemostasis can also be induced at much lower acoustic powers using microbubble cavitation [29, 30]. The work to date has focused on pre-clinical models, however if a robust portable device can be developed this technique could have a drastic impact on the treatment of trauma patients, especially in remote settings such as the battlefield.

Finally, ultrasound-mediated drug and gene delivery has many potential applications in the abdomen. Microbubbles loaded with drugs or genes can be destroyed in the target organ to locally deliver therapeutics while reducing the concentration in peripheral organs. One interesting application that is currently being researched is gene delivery to the pancreas [31]. Using this method, pancreatic islets have been regenerated *in vivo* in rats [32], suggesting a potential role for ultrasound in the treatment of diabetes. However, payload microbubbles for delivering a therapeutic have not been investigated in humans, and in many applications in the abdomen direct injection can be used to attain high local drug concentrations. Further, microbubbles loaded with therapeutics are typically custom and not commercially available, and therapeutic uses of microbubbles in general remain 'off-label'.

Cardiac

In the heart there is one FDA approved ultrasound device for the treatment of atrial fibrillation (Epicor, St. Jude Medical). The device is used intra-operatively to ablate tissue and disrupt the abnormal electrical circuits that cause atrial fibrillation, and many studies have reported positive outcomes using this device [33, 34, 35]. One major limitation of this device is that it is intraoperative and thus highly invasive. There is also significant competition with traditional surgery and other ablation methods, such as RF, which has limited broad clinical adoption of the device.

The heart is a challenging target for non-invasive or minimally invasive ablation because of the motion of the cardiac cycle and its position behind the rib cage, which limits the available acoustic window for an extracorporeal approach. A catheter HIFU device exists (ProRhythm) and has been investigated in humans for treating atrial fibrillation[36, 37]. The HIFU catheter device was expected to be an improvement over RF ablation for pulmonary vein isolation, producing more uniform lesions and reducing the risk of thrombus development. However, serious safety concerns due to the potential for esophageal heating leading to atrial-to-esophageal fistula have prevented further advancement of this technique. Following a patient death [38] changes were made to the device to bring the ultrasound focus closer to the catheter and reduce heating at the esophagus [37]. Despite this, and the implementation of a safety algorithm to reduce the ultrasound duty cycle as the esophageal temperature approached 40°C and terminate the ultrasound if the esophageal temperature was above 40°C, another patient death due to atrial-to-esophageal fistula occurred [39]. As a result of the safety concerns, this device is no longer in clinical use. Transesophageal devices, which focus the ultrasound energy away from the esophageal wall, thereby minimizing potential heating, may provide an alternative to endocardial catheter ablations that is still minimally invasive. These devices have been investigated numerically [40, 41] and in preclinical animal models [42, 43]. Transthoracic cardiac ablations in canine models have also been demonstrated [44, 45].

Cardiac ablation using ultrasound has been most widely investigated for treating atrial fibrillation, but can also be used for ablations to treat other cardiac arrhythmias, such as ventricular tachycardia [46]. Recently an epicardical catheter device has been investigated in swine [47], and an MR-compatible endocardial catheter has been developed and investigated in *ex vivo* tissues for tissue ablation monitored by MR thermometry [48] (Fig. 3). Endocardial RF catheter ablation for treating ventricular arrhythmias is very well established, but ablating targets deep in the heart wall or located behind scar tissue remains a challenge [49]. HIFU has the potential to be more effective in these cases, which could allow it to compete with RF.

Another proposed cardiac application of ultrasound is as an alternative to laser for transmyocardial revascularization. This has been investigated using the ultrasound to vaporize channels and cavities in the cardiac muscle [50]. However, more recently extracorporeal shockwave therapy, instead of tissue vaporization, has been proposed for this application [51]. In swine shockwave therapy has been shown to up-regulate vascular endothelial growth factors, which is believed to be one of the mechanisms through which it

promotes angiogenesis[52]. In patients with ischemic heart failure [53] and ischemia induced by coronary artery disease [54], shockwave therapy has produced positive results, improving angina scores [53, 54], perfusion [53] and left ventricular function [53]. Shockwave therapy can also elicit other beneficial responses from tissue. Low-energy shockwaves have been used to pre-condition the heart tissue prior to cell therapy to improve the left ventricular ejection fraction in chronic heart failure patients [55]. Based on work in animal models, the shockwaves appear to increase expression of chemoattractants [56], resulting in improved attraction of cells to the pre-treated tissue. Shockwave therapy is an attractive intervention because it is non-invasive and can be used for patients who are ineligible for other treatments. Two devices (Storz Medical, Switzerland; Medispec, USA) are currently CE approved for cardiac extracorporeal shockwave applications.

There are also a number of other non-thermal cardiac applications. Micro-ablation of the cardiac muscle using microbubbles has been proposed for tissue reduction therapy for patients with hypertrophic cardiomyopathy [57], and the mechanical fragmentation of the tissue using very short high intensity pulses, or histotripsy, may also have applications in tissue debulking [58]. In both cases these are cavitation-mediated processes. Drug and gene therapy, using the targeted destruction of payload microbubbles to deliver drugs and genes to the heart also relies on cavitation. One example of this is the delivery of agents to repair ischemic damage resulting from myocardial infarction. Delivery of stem-cell factor [59, 60] and stromal cell-derived factor [60] genes to the heart has been successful in promoting angiogenesis [59] and improving perfusion and heart function [60] in small animal models.

Shockwave and cavitation-mediated therapies have great potential in cardiac applications, but cavitation events in the heart can also produce premature complexes [61, 62, 63]. This can be seen as both a negative and positive effect. For example, when a contrast agent is used the pressure threshold for inducing these events is significantly reduced [62, 63], which is an important safety consideration for diagnostic imaging. However, it has also been shown in animal models that ultrasound can be used to pace the heart [64, 65]. Extracorporeal ultrasound could provide a non-invasive means for temporary cardiac pacing, providing an alternative to catheter, transcutaneous or epicardial pacing methods [65]. However, premature complexes resulting from ultrasound exposure have been linked to cardiomyocyte death [63], and it remains to be seen if ultrasound pacing would be safe over an extended period, or if it would remain effective.

Brain

The number of potential therapeutic applications of ultrasound in the brain continues to grow at a rapid rate as the potential of this method becomes more widely recognized. The adoption of phased array technology allowed a sharp ultrasound focus to be produced in spite of the sound aberrating effects of the skull bone [5, 66, 67], and the design of large aperture arrays [68, 69] solved the skull heating problem, making thermal ablation of central brain targets feasible. Figure 4 shows an illustration of a treatment setup for brain therapy with a large aperture array. A commercial clinical prototype array exists (ExAblate4000, InSightec) which operates at 650 kHz and has now been used for non-invasive brain ablation treatments in patients. The first reported functional neurosurgery application for this device

was for the treatment of chronic pain [70] and good pain relief at 1 year follow up has been reported [71]. In these first patients there was one reported complication of bleeding, which resulted in the addition of cavitation monitoring for future treatments with this device [71]. The ExAblate4000 has been used for the treatment of essential tremor [72, 73] which, similar to the treatment of chronic pain, involves targeting a portion of the thalamus for ablation. Excellent reduction in the tremor on the treated side has been reported, and the most commonly reported adverse effect appears to be persistent paresthesias [72, 73]. A multi-center trial is currently underway which should provide a more complete safety profile for this technique. This approach has been used in a small study with Parkinson's patients in Switzerland [74] and a trial has also begun at the University of Virginia and the Swedish Medical Center in Seattle, Washington.

The use of ultrasound for the treatment of ischemic stroke is another application that has been clinically investigated. Ultrasound can enhance the effects of lytic agents and has been investigated in humans in conjunction with tissue plasminogen activator (tPA) to increase its effectiveness [75, 76, 77]. These studies pre-date the use of large aperture phased arrays, and so the ultrasound was applied through the narrow temporal windows of the skull. However, one study that used low frequency planar ultrasound combined with tPA reported an increased risk of hemorrhage [76], and tPA alone has been associated with an increased risk of hemorrhage [78]. Researchers have thus sought to use ultrasound in the absence of a lytic agent to break down clots. Thus far, approaches using ultrasound alone [79, 80], as well as ultrasound combined with microbubbles [81], have shown potential for targeted recanalization of vessels in the brain. A recent study used perfluorocarbon droplets instead of microbubbles to facilitate clot breakdown [82]. The addition of droplets greatly reduced the power required to recanalize vessels in a rabbit model, compared with ultrasound alone [82], and since droplets only interact with the applied ultrasound where they are vaporized, they may reduce the risk of off-focus effects compared with microbubbles. The mechanism for the clot dissolution by ultrasound, or sonothrombolysis, is thought to be inertial cavitation [83]. The treatment of intracranial hemorrhage using MRI guided focused ultrasound has also been investigated in animal models, using FUS to dissolve large volume clots [84]. If the safety and effectiveness of sonothrombolysis using HIFU can be shown to meet acceptable standards for clinical investigations, there will still be a great challenge in making the technology accessible enough for it to be adopted into routine care. This is particularly an issue for the treatment of ischemic stroke, where there is a very limited time window for treatment following the stroke onset where permanent damage may be avoided.

Recent studies in rodents have used ultrasound to deliver genes [85] and erythropoietin (EPO) [86] to treat ischemic injury resulting from stroke. This is just one of many potential applications of drug delivery in the brain, a topic which has been heavily investigated in preclinical models. The presence of the Blood-Brain barrier (BBB), which is comprised of endothelial cells with limited active transport across the cell and tight junctions in the paracellular space [87], is a major roadblock for the treatment of neurological disorders. The BBB limits the molecules that can pass from the circulation to the brain tissue to small molecules (<400 Da) with high lipid solubility, preventing almost all large molecule drugs from reaching the brain in therapeutic quantities [88]. When combined with microbubbles, low intensity ultrasound can be used to transiently open the BBB and allow the passage of

agents that do not normally reach the brain tissue [89]. This has now been investigated in non-human primates [90, 91], including a thorough safety study using a commercial prototype array operating at 220 kHz (ExAblate4000 low-frequency system) and demonstrating repeat opening without negatively impacting cognition [91].

Ultrasound-mediated opening of the BBB (Fig. 4) has shown potential in several preclinical disease models. Delivery of amyloid-beta antibodies to a mouse model of Alzheimer's disease has been shown to reduce plaque number and size [92]. FUS alone has also been shown to reduce plaque load, possibly by facilitating the delivery of endogenous immunoglobulins to the brain [93]. In addition to reducing plaque load, FUS alone has been found to positively impact cognition, promoting neurogenesis [94, 95] and positively impacting memory in Alzheimer's transgenic mice [95]. Another potential application is for the treatment of Huntington's disease, which is caused by the mutation of the Htt gene. In mice, siRNA has been delivered to the brain using FUS, resulting in a decrease in Htt expression [79].

Finally, an interest in ultrasound neuromodulation has been revitalized long after early studies showed that ultrasound could induce reversible effects in cats [96]. In 2008, Tyler et al showed *in vitro* that low intensity ultrasound could stimulate electrical potentials in brain tissue [97]. Since then a number of animal studies have been performed, eliciting a range of responses [98, 99, 100], including in non-human primates [101]. A study has also been performed transcranially in healthy human volunteers, which reported that ultrasound modulates evoked potentials and can lower the sensory detection threshold [102]. However, the mechanism by which low intensity ultrasound modulates brain activity is poorly understood. One limitation of the published animal studies is that the ultrasound focus has been much larger than the brain structures being targeted. One recent study has tried to address this and reduced the focal volume using ultrasound modulation [103]. There is still a large amount of work to be done to reveal the full potential and limitations of ultrasound neuromodulation.

Extremities

Applications of ultrasound in the extremities include sonothrombolysis for deep vein thrombosis (DVT) [104, 105, 106] or peripheral artery occlusion [104]. For peripheral occlusions ultrasound has been applied with a catheter approach and, similar to stroke trials, has been used in combination with a lytic agent [104, 105]. Both the EkoSonic (EKOS Corporation, Bothell, WA, USA) and the OmniWave (OmniSonics, Lakewood, NY, USA) have regulatory approval in Europe and the USA for endovascular treatment of peripheral occlusions. In 2014 the EkoSonic system also received FDA approval for the treatment of pulmonary embolisms, using the same technique as for occlusions in the extremities. As an alternative to the catheter and lytic agent approach, a completely non-invasive approach using histotripsy pulses to break up clots has been demonstrated in pigs [106], but has not yet been investigated in humans.

Similar to the heart, shockwave therapy has been investigated in patients for treating the ischemic injury resulting from peripheral artery disease, and a reduction in the degree of stenosis and improvement in patient pain scores has been reported [107].

Low intensity, pulsed ultrasound (LIPUS) has also been shown to be effective for promoting bone healing [2]. LIPUS has been shown to improve healing rates for fresh fractures [2, 108, 109] and also appears to be effective in resolving delayed or non-unions [110, 111]. The Exogen Ultrasound Bone Healing System (Bioventus LLC, Durham, NC, USA) is approved in Europe and North America for treating non-unions and fresh fractures excluding skull and vertebrae. Results suggest that the Exogen system is as effective as electromagnetic stimulation, but has the benefit of a shorter treatment time for each session [111]

Cosmetic

Finally, several cosmetic applications of ultrasound have been developed. Termed 'microfocused ultrasound' (MFU), ultrasound at frequencies around 4–7 MHz has been used to created small thermal coagulation zones at depths of a few millimeters in order to tighten the skin. This has been used in patients for face and neck tightening [112], and more specifically to treat laxity in the lower eyelids [113]. However, there is strong competition in these applications from other non-surgical treatments, such as laser technology. In one application, ultrasound has been used alongside laser facial resurfacing to enhance transdermal cosmeceutical delivery [114]. Another cosmetic application that has been tested in humans is body sculpting, where high intensity FUS is used to ablate adipose tissue that is then later resorbed [115]. A randomized, sham-controlled body sculpting study found no difference in adverse events in the treated and sham groups at 24 week follow-up, suggesting that the treatment is safe [116].

Conclusion

Therapeutic ultrasound shows great potential for many clinical applications. To date, a number of applications have been clinically investigated in the abdomen, heart, brain and extremities. The number of new techniques and applications that are being developed in preclinical studies shows great promise for even wider adoption of ultrasound therapy. Moving forward, one challenge faced will be the need to translate developed methods into robust, affordable treatment platforms in order to ensure patient accessibility to ultrasound therapy.

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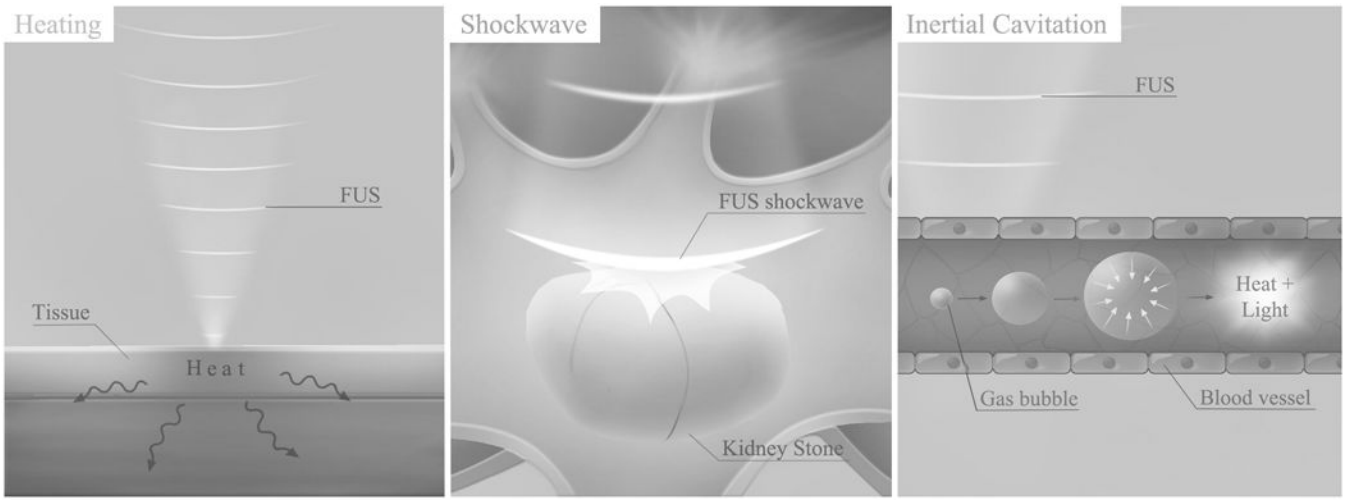

Figure 1.
Illustration of different treatment types. From left to right: thermal, shockwave and cavitation-mediated.

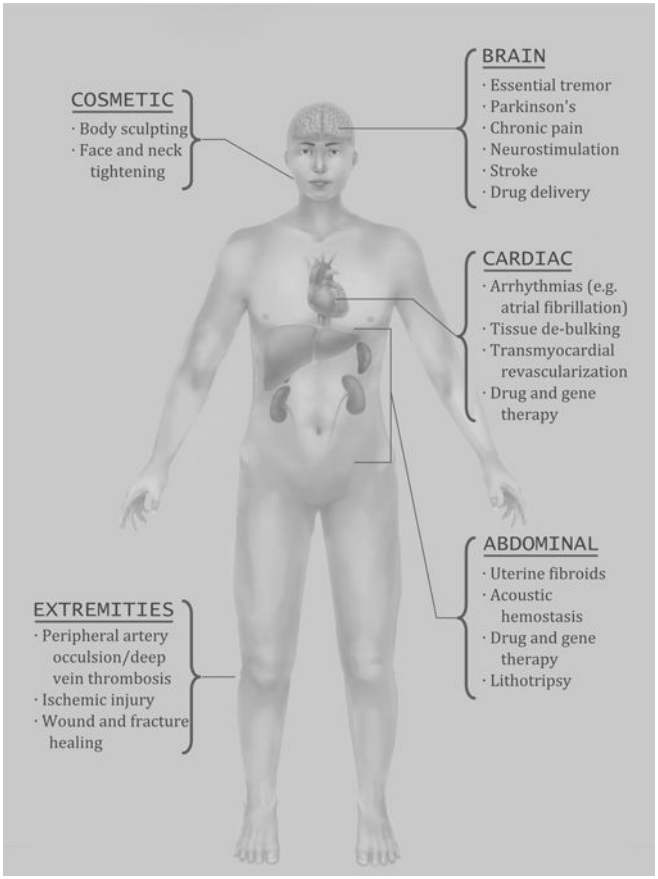

Figure 2.
Some applications of therapeutic ultrasound.

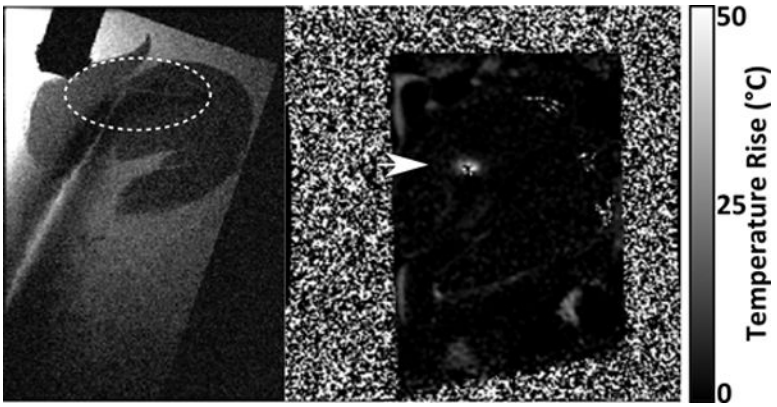

Figure 3.

(Left) Magnitude MRI image showing a steerable, MR-compatible endovascular HIFU catheter in an *ex vivo* porcine heart (white ellipse indicates catheter tip). (Right) MR thermometry image in a plane normal to the catheter tip showing the temperature rise in the heart wall. Courtesy of M. Carias.

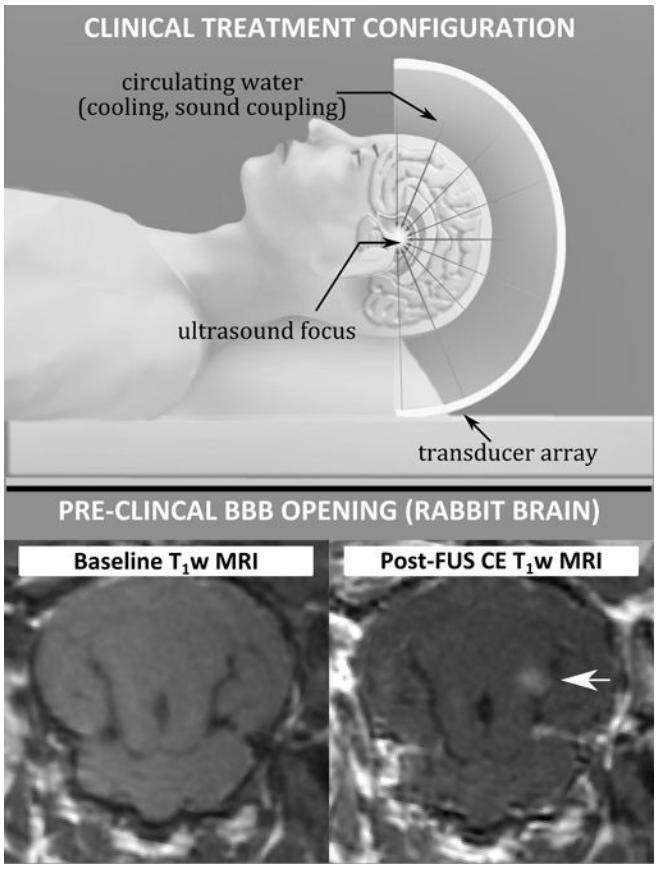

Figure 4.

(Top) Treatment setup for ultrasound therapy using a large aperture array. (Bottom) Baseline axial T_1-weighted MRI of a rabbit brain, and corresponding post-FUS, contrast-enhanced image showing enhancement indicating disruption of the BBB at the treated location (arrow).