International Congress on Ultrasonics, Universidad de Santiago de Chile, January 2009

Therapeutic ultrasound: Recent trends and future perspectives

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Abstract

Before ultrasound-imaging systems became widely available, ultrasound therapy devices showed great promise for general use in medicine. However, it is only in the last decade that ultrasound therapy has begun to obtain clinical acceptance. Recently, a variety of novel applications of therapeutic ultrasound have been developed that include sonothrombolysis, site-specific and ultrasound-mediated drug delivery, shock wave therapy, lithotripsy, tumor ablation, acoustic hemostasis and several others. This paper reviews a few selected applications of therapeutic ultrasound. It will address some of the basic scientific questions and future challenges in developing these methods and technologies for general use in our society. As a plenary presentation, its audience is intended for the ultrasound scientist or engineer, and thus is not presented at the level of the experienced medical ultrasound professional.

Introduction

Ultrasound is one of the most commonly used imaging modalities in all of medicine and is particularly well known for its ability to image the developing foetus; however, ultrasound offers an enormous, and so far mostly unrealized, potential for image-guided therapy.

This potential was anticipated more than 50 years ago, before diagnostic ultrasound had achieved even an early stage of development, when the Fry brothers were able to use High Intensity Focused Ultrasound (HIFU) to perform "surgery" on patients with Parkinson's disease. Recently, therapeutic ultrasound is being investigated in a number of modalities for the treatment of a variety of medical conditions; for example, see the excellent review by Mitragotri [1]. For reference, Fig. 1 shows a sketch of the acoustic parameters associated with therapeutic ultrasound and their approximate value for a few specific applications. This paper addresses a few of the topics presented in a general

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plenary lecture given at the 2nd ICU in Santiago, Chile, and is intended as a brief review of some selected topics in therapeutic ultrasound for the ultrasound scientist or engineer, and not for the specialist in medical ultrasound.

Fig.1　Some representative acoustic parameters.
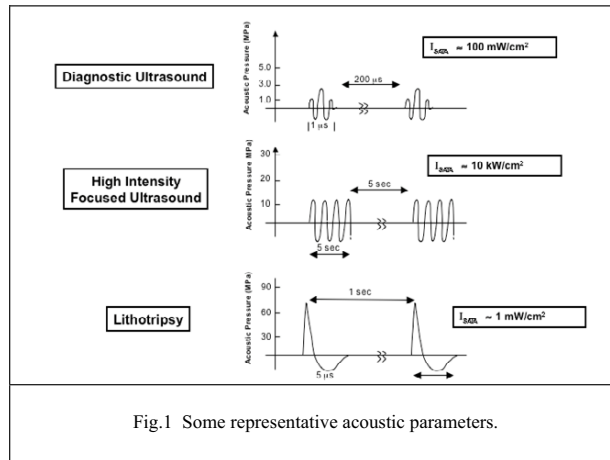
Sonothrombolysis

Although we can not survive without blood flowing though our vascular system, blood clots are a major nemesis, causing infarctions in the heart and blockages in the brain; indeed, strokes are the leading cause of disability in the United States. Doppler ultrasound is well known for its ability to image the entire vascular tree, and major progress is being made in the use of ultrasound for both imaging of the clot, as well as inducing or accelerating clot lysis. A now famous study was conducted by Alexandrov, *et al*. [2] which demonstrated that the use of transcranial Doppler ultrasonography combined with a thrombolytic drug (t-PA) could significantly improve the recanalization rate of the blocked artery or result in a dramatic clinical recovery of the patient. This important discovery has accelerated a number of investigations into the use of ultrasound for clot dissipation, an area of research called "sonothrombolysis", see for example [3]. In particular, considerable efforts are focused on this non-invasive approach to clot dissolution.

Although there is great interest in the clinical application of sonothrombolysis, there are still unanswered questions concerning the physical mechanisms that give rise to this effect. Ultrasound, by itself, should not exhibit significant forces on a clot, at least to first order; it is the difference in acoustic impedance that results in radiation force, and a clot's acoustic impedance would differ only slightly from that of the surrounding blood. Of course, acoustic streaming can occur in blood due to the absorption of sound [4], but it is difficult to obtain significant streaming with a Doppler waveform alone. On the other hand, if microbubbles are present, then streaming can be greatly enhanced [5] due to the strong radiation forces exerted by ultrasound on bubbles, as well as microstreaming induced by the pulsations of the bubbles themselves; thus, there is significant research activity in the combined use of ultrasound contrast agents (stabilized microbubbles) together with pulsed ultrasound, with and without a thrombolytic drug. It is likely that when ultrasound is combined with t-PA alone (no ultrasound contrast agents), there are sufficient cavitation nuclei in the host fluid itself to induce some level of radiation-force type streaming. A second concept that may be important is one generally termed "pulsatility" [6], in which the PRF of the Doppler signal could induce a pulsation of the clot. Under this scenario, the clot could be distorted under the action of radiation force and pump the drug in and out of the clot—which should result in increased lysis. If such a scenario exists, then modifying the PRF until maximum pulsatility is achieved (which can be measured with ultrasound) should result in increased clot lysis.
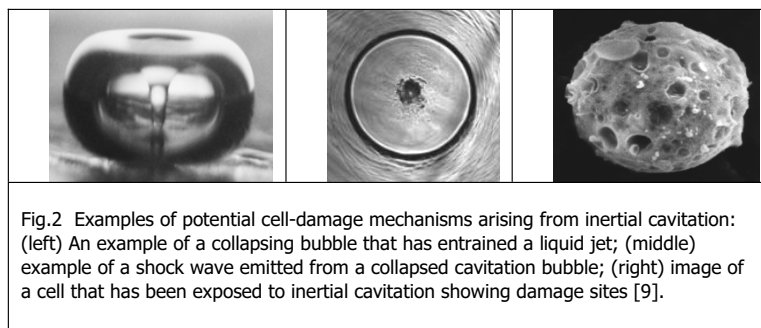
Finally, although non-invasive approaches are particularly attractive, there are FDA-approved minimally-invasive devices, such as the EKOS series of transducer-tipped catheters, that have been proven effective for sonothrombolysis [7].

Ultrasound-enhanced drug delivery

Genetic engineering offers great promise for significant advances in health care and the treatment of a number of diseases. In order to treat hereditary genetic disorders, such as haemophilia, the defective gene must be replaced within the DNA of the defective cell nucleus. If the cell can then express this repaired DNA, by transfection of the missing protein, such as Clotting Factor VIII for haemophilia, then the disease can theoretically be cured [8]. The most common approach for this gene insertion is to modify a virus, which has evolved to reproduce only by managing to insert itself and its genetic material into the nucleus. However, viral-based gene therapy has had its setbacks and alternative approaches are being sought. One approach is to use ultrasound to transiently open the cell membrane, thus permitting the genetic material to be taken up by the cell. This temporary, ultrasound-induced, cell permeability is typically called sonoporation, and this general approach ultrasound-enhanced drug delivery. Of course, one can also envision using this uptake of drugs to kill the cell, as in the treatment of benign and malignant tumors.

There has been considerable research activity directed toward the understanding of the basic physical mechanisms that gives rise to transient cell permeability. It is believed that the principal mechanism is cavitation, although there is some disagreement as to the specific type of cavitation that results in sonoporation. For example, if the acoustic driving pressure is sufficiently high, a gas-filled nucleation site will grow to several times its initial radius and collapse with considerable violence. If the collapse depends more on the mass of liquid surrounding the bubble than on the stiffness of the gas contained within the bubble, this type of cavitation is termed "inertial cavitation" and the event typically lasts for only a few cycles.   When the source pressure is low, and the bubble's collapse is controlled by the stiffness of the gas, this type of cavitation is called "stable cavitation" and the bubble typically survives for thousands of cycles. These two different types of cavitation would induce sonoporation in different ways.

Shown in Fig. 2 is an example of inertial cavitation and it potential for affecting cells.

Fig.2 Examples of potential cell-damage mechanisms arising from inertial cavitation: (left) An example of a collapsing bubble that has entrained a liquid jet; (middle) example of a shock wave emitted from a collapsed cavitation bubble; (right) image of a cell that has been exposed to inertial cavitation showing damage sites [9].

If the bubble collapse is violent, and near a boundary, high-speed liquid jets can develop at the final stages of collapse which can penetrate several jet diameters into solid metal. If the collapse is spherical, strong shock waves can develop which also have the capability of damaging nearby interfaces. Thus, inertial cavitation most certainly has the capability to induce membrane permeability in cells in the vicinity of cavitation.
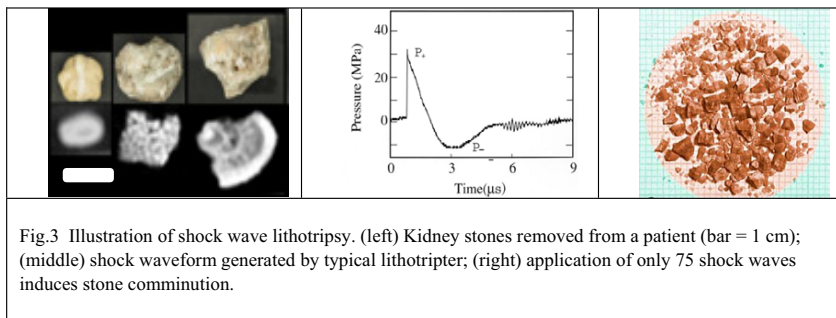
If one is interested in destroying cells, then cavitation can be very effective, at least in an *in vitro* suspension. However, if one wishes to use ultrasound for gene therapy, then it is important not to kill the cell, but to induce it to take up genetic material, survive, undergo transfection and express (produce) the desired protein. In this case, one wants only to slightly injure the cell and induce cell permeability. Probably the best way to do this is to use stable cavitation, wherein the shear forces induced by acoustic streaming in the vicinity of the oscillating bubble can permeabilize the cell membrane. Some recent results by Forbes, *et al.*, [10] suggest that the threshold for sonoporation is lower than that for inertial cavitation, and the yield is higher when only stable cavitation is

produced. On the other hand, Miao, *et al*., [8] have demonstrated that intensities much higher than the inertial cavitation threshold are necessary when gene transfection is to be produced *in vivo*. Suffice it to say that this is an active area of research with considerable promise for clinical applications.

Shock Wave Therapy; Lithotripsy

Kidney stones afflict 13% of men and 7% of women in the U.S., and comparable statistics apply worldwide. The prevalence of kidney stones varies dependent on race, sex, age, and geographic location; however, stone formers can be any age, and many develop multiple stones at a time. Some stones pass spontaneously; however, those that don't account for 1% of all hospitalizations annually in the U.S.

Shock Wave Lithotripsy is the most common treatment used for stone disease today. Shock waves generated outside the body are focused to a fixed location. The patient, usually under anaesthesia or conscious sedation, is positioned with the stone within this focal zone. Between 1500 and 4000 shock waves are applied at about 2 Hz (range 1-4 Hz).

Fig.3 Illustration of shock wave lithotripsy. (left) Kidney stones removed from a patient (bar = 1 cm); (middle) shock waveform generated by typical lithotripter; (right) application of only 75 shock waves induces stone comminution.
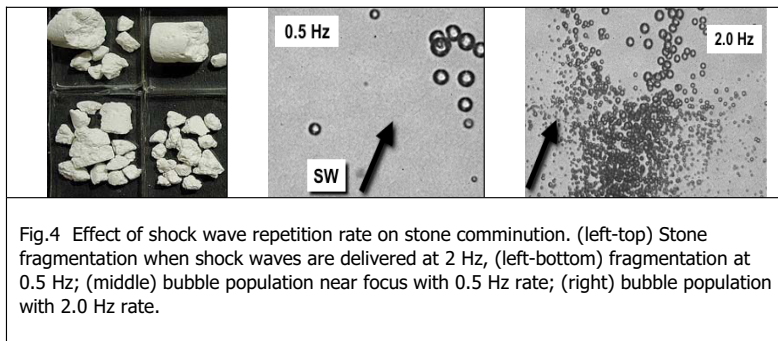
The shock waves travel through water into the body. In the original lithotripter, the Dornier HM-3, the patient rested in a water bath. All current lithotripters have the SW source enclosed in a water-filled pillow that is coupled to the patient's skin. Treatment outcome is measured by stone-free rates after 1 to 3 months, and by re-treatment rates. Stone-free rates range from 40-90% with different machines; newer machines have lower stone-free rates and higher re-treatment rates. Fig. 3 shows some results of a typical lithotripter application.

When a shock wave with a very rapid rise time (< 50 ns), a positive pressure amplitude of 35 MPa, and a negative pressure amplitude of about 10 MPa is delivered to a stone, it breaks into many small pieces, typically in less than 100 shock waves. However, a typical clinical treatment usually results in over 1000 shock waves delivered. Of course, if the stones are not broken until each fragment is less than about 2 mm, natural stone passage can be complicated.

There is a continuing disagreement on the actual mechanism that results in stone comminution. Since the typical shock wave used in lithotripsy has a negative pressure in excess of 10 MPa, cavitation is not only likely to be present, but also to be quite violent. It is thus not unreasonable to expect that cavitation plays a significant role in stone comminution [11]. When a shock wave reflects from an interface, negative pressures can be doubled, and spallation is a well-known mechanism for material fracture. However, Sapozhnikov *et al.*, [12] have developed a numerical model for shock wave propagation in synthetic stones and determined that the highest tensile stress developed within the stone results from shear waves initiated at the proximal corners of the stone, and that spallation results in considerably lower tensile stresses. Novel experiments that isolated the various stress contributions were performed that supported the modelling results. These various experimental and numerical studies suggest that shear waves result in the initial fragmentation of the stone into smaller pieces, but cavitation plays a much larger role in further reducing the sizes of the fragments into those that would naturally pass through the urinary tract.

An important discovery in lithotripsy research is that reducing the shock wave repetition rate from 2 Hz (a commonly used rate) to 0.5 Hz significantly improves stone comminution, and interestingly, also reduces tissue damage [13].

Fig.4 Effect of shock wave repetition rate on stone comminution. (left-top) Stone fragmentation when shock waves are delivered at 2 Hz, (left-bottom) fragmentation at 0.5 Hz; (middle) bubble population near focus with 0.5 Hz rate; (right) bubble population with 2.0 Hz rate.
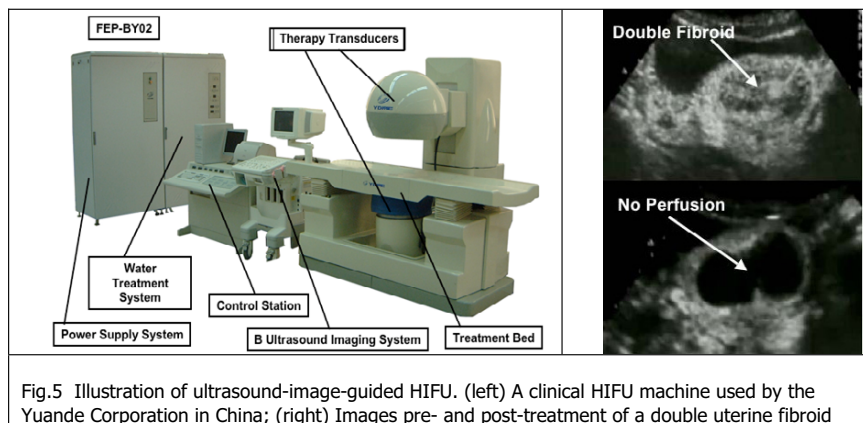
Shown in Fig. 4 is an illustration of this effect and some evidence that it is due to screening of the stone by cavitation bubbles produced by the shock waves. Once a shock wave propagates through a liquid, the cavitation produced can transfer dissolved gas from the liquid into free gas in the bubble, through a process generally termed rectified diffusion. Once these bubbles are formed, they slowly dissolve, but if a second pulse arrives before the bubbles from the previous cavitation event have not yet dissolved, then these daughter bubbles act as cavitation nuclei and more bubbles are produced. Once a large number of bubbles are present in the shock wave path, screening of the stone from the shock wave can occur.

High Intensity Focused Ultrasound

One of the most promising applications of therapeutic ultrasound is that of image-guided therapy in which High Intensity Focused Ultrasound (HIFU) is used to ablate benign and malignant tumors through a completely non-invasive procedure. Although neither magnetic resonance nor ultrasound imaging was available at the time, non-invasive HIFU was used to treat patients with Parkinson's and other neurological diseases by the Fry brothers over 50 years ago [14]. With the advent of the increased capabilities of diagnostic ultrasound, Chinese investigators developed ultrasound-guided HIFU in the late 1990s and tens of thousands of patients have been treated to date [15]. Because it is possible to perform thermometry with MR imaging, the first device approved in the United States uses MR-guidance [16], and patients are routinely being treated for uterine fibroids [17].

An illustration of one particular ultrasound-guided system in current use in China, and in our laboratory, is given in Fig. 5. Using ultrasound imaging, one can clearly distinguish targets of interest, such as a uterine fibroid, provided there is a readily-available acoustic window. This clinical system uses a high-end diagnostic ultrasound system to locate the tumor, and then a focused ultrasound transducer to target the tumor and supply the HIFU necessary for   thermal ablation. Although the intensities used in these systems are high enough to produce cavitation, this phenomenon probably doesn't play a major role in ablation. Indeed, when HIFU is applied to tissue, it is not uncommon to see hyperechoic regions in the image that might be interpreted as cavitation [18], although recent studies suggest that these hyperechoes are most probably gas and vapor produced by boiling [19].

One of the challenges of using a completely non-invasive ablation approach is that it is difficult to determine the end result of a HIFU treatment. Various approaches are used but most of them involved pre-and post contrast imaging.

Fig.5 Illustration of ultrasound-image-guided HIFU. (left) A clinical HIFU machine used by the Yuande Corporation in China; (right) Images pre- and post-treatment of a double uterine fibroid

showing that HIFU-induced ablation essentially stops vascular perfusion.

It is presumed that in a successful treatment, the tumor and a surrounding margin is completely ablated by the HIFU, through a process called coagulative necrosis. In this scenario, the tissue is heated to the point for which protein denaturation occurs, and thus the tissue and blood is irreversibly damaged (like cooking an egg). One can thus determine, to some extent, the region of complete ablation by imaging the region of interest with a contrast agent that is carried by the blood. Presumably, if the blood supply to a tumor is terminated, then the tissue must either be dead, or will soon die. An illustration of this effect is shown in Fig. 5 in which two uterine fibroids were treated with an ultrasound-image-guided HIFU system. Before the treatment, the fibroids were imaged with ultrasound, using an ultrasound contrast agent (stabilized microbubbles); after treatment, the treated region shows no contrast agent uptake, thus indicating that the tumor's blood supply has been stopped.

It is possible to imagine a large number of applications of image-guided therapy and research in this area is rapidly expanding. One application that has captured our own interest is the use of HIFU to terminate bleeding, an application that we call "acoustic hemostasis". Our research has demonstrated the successful use of HIFU to induce hemostasis in a number of cases [20, 21]. In this last example of therapeutic ultrasound, we show an example of its use in trauma. When individuals are involved in automobile accidents, high decelerations often occur (one collides with another vehicle). Since the liver is a large organ, is highly perfused with blood, and can not sustain high shear loads (it tears easily), it is not uncommon for uncontrolled bleeding of the liver (and spleen) to occur in patients who have been involved in an automobile accident. Unless this bleeding can be stopped, exsanguination (bleeding to death) can result. Indeed, exsanguination is the principal cause of death in combat [22] and is a large fraction of those dying from blunt trauma [23]. Shown in Fig. 6 is an illustration of how image-guided HIFU can be used to treat bleeding in a porcine animal model.
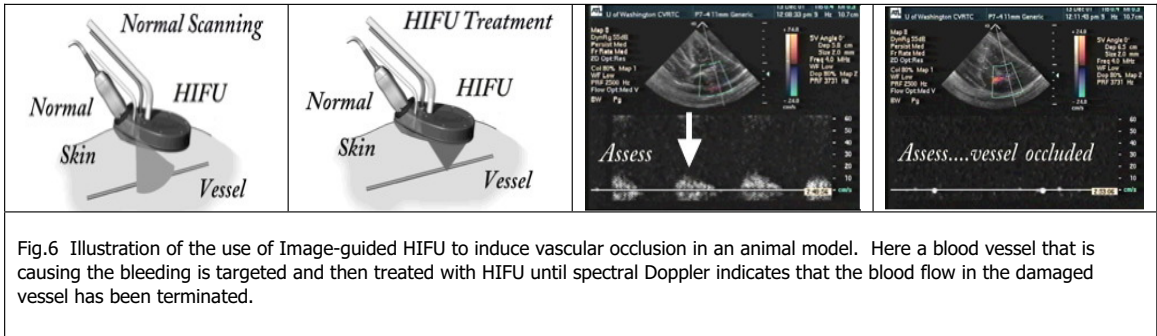

Fig.6 Illustration of the use of Image-guided HIFU to induce vascular occlusion in an animal model. Here a blood vessel that is causing the bleeding is targeted and then treated with HIFU until spectral Doppler indicates that the blood flow in the damaged vessel has been terminated.

In this example of image-guided acoustic hemostasis, an ultrasound scan is made of the liver, the (bleeding) vessel of interest targeted, and HIFU applied, in an effort to reduce the bleeding. Spectral Doppler, which can measure flow rate, is used to monitor the progress of the therapy. In a real case of trauma, a first responder would first try to find the major "bleeder" and apply pressure so as to reduce the blood flow. If "haemorrhage control" can be achieved, providing sufficient time to transport the injured patient to the operating room, then patient survival rates could be significantly improved. With ultrasound, one can use Doppler imaging to detect bleeding because the entire vascular tree can be imaged. It is also possible to apply certain imaging algorithms to determine if a particular branch point in the vascular tree is a normal connected one or one that is open and bleeding.

Summary

In this paper, we have provided a few examples of the current trends in the use of therapeutic ultrasound in medicine, and some discussion of its potential for widespread use. The major promise of this new non-invasive technology is to introduce methods and approaches that now do not exist, and/or to reduce the morbidity associated with conventional therapy. A large percentage of operations are now being performed using laparoscopic procedures that significantly reduce morbidity, and hospital stays associated with invasive surgery. It is only reasonable that completely non-invasive procedures are the natural progression of these new and emerging technologies, and the operating room of the future may well be a hand-held image-guided therapy system not unlike the "tricorder" of Star Trek fame.

Acknowledgement

References

[1]. S. Mitragotri, "Healing sound: the use of ultrasound in drug delivery and other therapeutic applications", *Nature Reviews: Drug Discovery,* **4**, 255-260 (March 2005).
[2]. A. V. Alexandrov, A. M. Demchuk, R. A. Felberg, I. Christou, P. A. Barber, W. S. Burgin, M. Malkoff, A. W. Wojner, and J. C. Grotta, "High Rate of Complete Recanalization and Dramatic Clinical Recovery During tPA Infusion when Continuously Monitored with 2-MHz Transcranial Doppler Monitoring", *Stroke*, **31**, 610-615 (2000).
[3]. "1st International Sonothrombolysis Conference", S. Meairs and A. V. Alexandrov, eds., *Cerebrovascular Diseases*, **26**, (2008) Suppl. 1.
[4]. X. Shi, R. W. Martin, S. Vaezy and L. A. Crum, "Quantitative investigation of acoustic streaming in blood", *J. Acoust. Soc. Amer. Am.,* **111**, 1110-1125 (2002).
[5]. C. K. Holland, S. S. Vaidya, S. Datta, C. C. Coussios, and G. J. Shaw, "Ultrasound-enhanced tissue plasminogen activator thrombolysis in an in vitro porcine clot model", *Thromb Res.,* **121**: 663–673 (2008).
[6]. J. Kucewicz, B. Dunmire, N. Giardino, D. Leotta, M. Paun, S. Dager, and K. Beach, "Tissue Pulsatility Imaging of Cerebral Vasoreactivity During Hyperventilation", *Ultrasound in Medicine & Biology*, **34**, 1200-1208 (2008).
[7]. B. R. Mahon, G. M. Nesbit, S. L. Barnwell, W. Clark, T. R. Marott, A. Weill, P. A. Teal and A. I. Qureshi, "North American Clinical Experience with the EKOS MicroLysUS Infusion Catheter for the Treatment of Embolic Stroke", *American Journal of Neuroradiology,* **24**, 534-538 (2003).
[8]. C. H. Miao, A. A. Brayman, K. R. Loeb, P. Ye, L. Zhou, P. Mourad, and L. A. Crum,"Ultrasound enhances gene delivery of human factor IX plasmid", *Hum Gene Ther*. **16**, 893-905 (2005).
[9]. Y. Taniyama, K. Tachibana, K. Hiraoka, M. Aoki, S. Yamamoto, K. Matsumoto, T. Nakamura, T. Ogihara, Y. Kaneda and R. Morishita, "Development of safe and efficient novel nonviral gene transfer using ultrasound: Enhancement of transfection efficiency of naked plasmid DNA in skeletal muscle", *Gene Therapy*, **9**, 372-380 (2002).

[10]. M. Forbes, R. Steinberg, W. O'Brien Jr., "Examination of Inertial Cavitation of Optison in Producing Sonoporation of Chinese Hamster Ovary Cells", *Ultrasound in Medicine & Biology*, **34**, 2009-2018 (2008).

[11]. L.A. Crum, "Cavitation microjets as a contributory mechanism for renal calculi disintegration in ESWL," *J. Urology*, **140**, 1587-1595 (1988).

[12]. O. A. Sapozhnikov, A. D. Maxwell, B. MacConaghy, and M. R. Bailey, "A mechanistic analysis of stone fracture in lithotripsy", *J. Acoust. Soc. Am.* **121** 1190-1202 (2007).

[13]. R. F. Paterson, D. A. Lifshitz, J. E. Lingeman, A. P. Evan, B. A. Connors, N. S. Fineberg, J. C. Williams, J. A. McAteer, "Stone fragmentation during shock wave lithotripsy is improved by slowing the shock wave rate: Studies with a new animal model", *J Urology.*, **168**, 2211-2215 (2002).

[14]. W. J. Fry and F. J. Fry, "Fundamental neurological research and human neurosurgery using intense ultrasound," *IRE. Trans. Med. Electron*, Vol. ME-7, 166-181 (1960).

[15]. F. Wu, Z. B. Wang, W. Z. Chen, J. Z. Zou, J. Bai, H. Zhu, K. Q. Li, F. L. Xie, C. B. Jin, H. B. Su, and G. W. Gao, "Extracorporeal focused ultrasound surgery for treatment of human solid carcinomas: early Chinese clinical experience," *Ultrasound in Medicine & Biology*, **30**, 245-260 (2004).

[16]. K. Hynynen, V. Colucci, A. Chung, and F. Jolesz, "Noninvasive arterial occlusion using MRI-guided focused ultrasound," *Ultrasound in Medicine & Biology,* **22**, 1071-1077 (1996).

[17]. G. K. Hesley, K. R. Gorny, T. L. Henrichsen, and D. A. Woodrum, "A clinical review of focused ultrasound ablation with magnetic resonance guidance: An option for treating uterine fibroids," *Ultrasound Quarterly,* **24***,* 131-139 (2008).

[18]. L. A. Crum and W. Law, "The relative roles of thermal and nonthermal effects in the use of high intensity focused ultrasound for the treatment of benign prostatic hyperplasia," Proceedings of the 15th Intern. Congr. on Acoustics (Trondheim, Norway): 315–319 (1995).

[19]. V. A. Khokhlova, M. R. Bailey, J. A. Reed, B. W. Cunitz, P. J. Kaczkowski, and L. A. Crum, "Effects of nonlinear propagation, cavitation, and boiling in lesion formation by high intensity focused ultrasound in a gel phantom," *J. Acoust. Soc. Am.*, **119**, 1834-1848 (2006).

[20]. S. Vaezy, R. W. Martin, P. Kaczkowski, G. Keilman, B. Goldman, H. Yaziji, S. Carter, M. Caps, and L. A. Crum, "Use of High Intensity Focused ultrasound to control bleeding", *Yearbook of Vascular Surgery*, 2000.

[21]. W. Luo, V. Zderic, S. Carter, L. A. Crum, and S. Vaezy "Contrast-Enhanced Bleeding Detection of a Punctured Femoral Artery", *J Ultrasound Med*., **25**, 1169-1177 (2006).

[22]. R. Zajtchuk and G. R. Sullivan, "Battlefield trauma care: Focus on advanced technology", *Military Medicine*, **160**, 1-7 (1995).

[23]. C. B. Anderson and W. F. Ballinger, "Abdominal injuries. in *The Management of Trauma.* 3rd Ed., G. D. Zuidema, R. G. Rutherford and W.F. Ballinger editors, WB Saunders Co., Philadelphia, PA: (1979).