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Editorial

Image-Guided Focused Ultrasound: Endless Possibilities for Non-Invasive Therapy in the 21st Century

Victor Frenkel*

Department of Biomedical Engineering, Catholic University of America, USA

Corresponding author
Victor Frenkel, Department of Biomedical Engineering, Catholic University of America, USA, Email: FRENKEL@cua.edu

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A man arrives at a university hospital. He suffers from essential tremor (ET), a neurological disorder characterized by involuntary and rhythmic shaking during voluntary movements such as lifting a cup to drink. The MR scanner in which he is placed looks like any other scanner you would find in a hospital or clinic. It has however one major difference. At the end of the patient table is a large helmet-shaped device, inside of which is a sophisticated array of ultrasound transducers. As he lies down on the table, the device is placed over his head, and coupled to this scalp with a flexible water jacket.

This is not science fiction. And it's also not a prediction of what visionaries are saying is inevitable for medical science. It's a Monday. June 20th, 2011. And our patient is about to undergo a revolutionary procedure that's been in development for almost a century.

Back to our device, which admittedly looks like something you'd see in a B-rated science fiction movie. One of its unique features is that the ultrasound beams created by each of the more than 1000 individual transducers are incapable of creating any effects in the tissues on their own. At the point, however, where the beams intersect, the concentration of acoustic energy can raise the temperature of the tissue and destroy it within just seconds. This focal point, just millimeters in diameter, can also be electronically steered and accurately positioned at any location within the brain. In this particular treatment, the target is the thalamus; the region associated with ET.

Still sound like science fiction? Please read on.

But first a little history: More than half a century before, in the early 1940's, the first study was published demonstrating how a focused ultrasound (FUS) beam can generate a biologically significant effect. Experiments in mid-sized animal models indicated that reversible changes could be created in the brain, identified by well characterized modifications in behavior. The importance of not creating any effects in the intervening tissues was also notable, being an essential prerequisite for future clinical translation. More than a decade later in the mid 1950's William and Francis Fry from the University of Illinois showed that these exposures could be carried out in humans. The need for image-guidance however now became evident. And it was not until the first image-guided devices were developed that FUS ablation became clinically feasible.

Back in the MR scanner, after a sequence of well practiced safety checks, the ET patient is now ready to be treated. The tests included a short, low energy FUS pulse that generates a temperature elevation of only a few degrees Celsius. This is viewed using a special sequence exclusive to MRI where a temperature 'map' is superimposed on a pre-scanned MR image. This short-lived and minimal temperature elevation is inferred from a predictable change in the motion of the protons of the body's molecules in response to being heated. It is inconsequential from a biological perspective. However, it's essential to ensure that the beam's focus is directed at the correct location.

The safety and accuracy of these FUS treatments has continued to improve since the first CE approved procedure in Europe in the early 1990's. This was for the ablation of prostate tumors using a trans-rectal FUS device guided with a coaxial ultrasound imaging transducer. Just over a decade later, the FDA approved the first treatments of uterine fibroids using an MR guided FUS system. Today there are hundreds of centers world-wide with similar systems, where tens of thousands of these procedures have already been safely carried out. The ability to successfully combine state of the art MR imaging with sophisticated FUS devices paved the way to undeniably the most challenging of these noninvasive surgical procedures: ablation of highly localized regions in the brain.

What truly can be characterized as nothing short of amazing is that this noninvasive surgery is being carried out in the ET patient who is awake and fully alert. Further making this procedure appear to be something from the future is that the physician's only instrument is a computer mouse, which he uses at the modified MR console. He is also 15 feet from the patient and in an adjacent room. After a traditional MR scan is carried out to identify the region in the thalamus to be treated, the safety exposure is performed and the patient is now ready for treatment. A number of final adjustments are made on the

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graphic user interface, which are then followed by one final click of the mouse. Within seconds the tissue is heated to just above 60 degrees Celsius. The proteins are denatured and the exposed cells destroyed. The MR thermometry sequence validates that indeed the required thermal dose was delivered to the 3 mm diameter region. And then the patient is taken out of the scanner and, after a short post-op monitoring period, he is free to go home.

Another one of the debilitating manifestations of ET affecting quality of life is the inability to write in a legible manner. In order to evaluate the immediate benefits of the FUS treatment, the patient was asked to write a simple sentence before and after he was treated. The stark difference in improvement in his handwriting afterwards was an undeniable testament to the success of the procedure. His wife's reaction pretty much summed it up, stating simply and to the point that it was 'miraculous'.

This ground-breaking sequence of events was documented in a video by the popular site, Technology Entertainment Design (TED), logging over 100,000 views in its first five days. Two years later, it stands at over a half a million. This exemplifies the interest and excitement that exists today for this technology, which is no longer considered obscure, and instead is fast becoming mainstream. As a personal testimony, when I first started my graduate studies in this field almost two decades ago, my friends and colleagues saw therapeutic ultrasound (TUS) as no more than a curiosity. Today, of course, the reactions are quite different.

This revolutionary treatment of ET is emblematic of the extraordinary variety of procedures presently being carried out and in development employing image-guided FUS. As astonishing as these results were to the average layman, who saw a man walk in to a clinic with an incurable and life altering neurological disorder, and then walk out completely cured a few hours later, they were not to my colleagues and me. Over the years we have witnessed the deliberate and incremental progress in this field, as we made our own contributions. In 2002 there were just over 250 publications on FUS related studies. Ten years later, in 2012, there were more than 1100.

Using ultrasound for therapeutic purposes dates back more than half a century, even predating its use for diagnostic imaging. TUS can generally be described as the use of ultrasound for applications other than imaging or diagnostics. In diagnostic ultrasound, energy deposition in the tissues is meant to be minimal in order to prevent the occurrence of adverse biological effects. Applications of TUS, on the other hand, are based on depositing ultrasound energy to specifically create effects. These effects can be mild and reversible, such as those employed by physical therapist for the purpose of healing. Or they can be more extreme and irreversible such as FUS employed for the treatment of the ET. Here, focusing the beam can concentrate the energy, allowing heat to be generated faster than it can be removed. As a consequence, the tissue is ablated by the process of coagulative necrosis.

It was just over sixty years ago when TUS exposures were first shown to be beneficial in routine medical practice. In a seminal preclinical study, low energy, non-focused exposures were shown to stimulate the formation of bone callus in a radial fracture model in rabbits. Since then, interest and development in the field of TUS has continued to grow, where presently hundreds of research centers and universities world-wide are working to develop and improve applications in the fields of vascular disease, oncology, cellular therapy and physical therapy. Whereas non-focused, low intensity TUS exposures are being used in the clinic for healing and to enhance local transdermal delivery, FUS is being employed for thermally ablating uterine fibroids and a variety of malignant tumors including those in the prostate, breast, pancreas, and bone.

Some of the most exciting new applications of FUS involve providing these exposures at energy levels that fall somewhere between those for physical therapy and ablation. By employing these FUS exposures in pulsed mode (pFUS) temporal rates of energy deposition are substantially decreased, and cooling can occur between the individual pulses. As a result, temperature elevations can be restricted to just a few degrees Celsius and non-thermal mechanisms of ultrasound interactions with the tissues can predominate. Today, these pFUS exposures are being developed for a variety of drug delivery applications, including enhancing the penetration of thrombolytics in to blood clots, opening the blood-brain-barrier to enable the delivery of agents to the brain, and facilitating the delivery of chemotherapeutic agents in to solid tumors. Additional applications in development for pFUS include blocking nerve conduction to control spasticity, and remote palpation for diagnosis of tumors and liver sclerosis.

One of the exciting new directions getting a lot of attention in the TUS research community is combining pFUS exposures with specialized drug carriers to maximize local deployment of agents in a targeted region. This type of strategy is extremely advantageous in the case of chemotherapeutic agents because of their notoriously toxic nature to healthy, non-cancerous cells. A number of years ago, my colleagues and I first demonstrated how pFUS exposures could be used to deploy an FDA approved chemotherapeutic agent from temperature sensitive liposomes (TSLs). The TSLs were administered systemically in a small animal model with a tumor on its flank. The pFUS exposures, provided only in the tumors, were designed to generate non-destructive temperatures of only a few degrees Celsius; just enough to render the liposomes leaky and release their payload. The success of this study has lead to dozens of similar studies being carried out. And today clinical trials with this procedure are already being planned.

As for the future, it is equally promising. One hot topic is the development of hand-held devices for delivering personalized treatment at the bedside. Similar to the state-off-the-art MR guided FUS systems, these small and compact devices also combine the newest ultrasound transducer technology with sophisticated and high resolution, real-time, image guidance and monitoring capabilities. My colleagues and I recently evaluated one such device that we developed. In a preclinical, arterial bypass graft model of chronic thrombus, we demonstrated how pFUS exposures provided with this device could facilitate improved recanalization of the clotted vessel with an FDA approved thrombolytic. Whereas treating an acute blood clot in the brain, as occurs in the case of an ischemic stroke, would require the more advanced imaging capabilities of an MR guided system, these relatively inexpensive and hand-held devices could be perfectly suitable for recurring treatments in the legs of a bed-ridden patient suffering from deep vein thrombosis (DVT).

Another exciting investigational direction that is truly pushing the boundaries for potential applications is based on the molecular effects that these FUS exposures can generate. A variety of studies have already reported increased expression levels of genes for which a host of therapeutic applications could be proposed. This includes genes for enhancing revascularization of ischemic tissue, for controlling the expression of exogenously administered therapeutic genes, and even for increasing targeting of stem cells to a designated tissue or organ. Indeed, for all three of these exciting applications, the proof-of-concept studies have already been carried out and published.

So back one last time to check in on our ET patient. Two years later and he's doing just fine. Playing golf, and in general, enjoying his retirement. Only 10 years ago, however, before the first FDA approval of an MR guided FUS device, his prognosis would not have been so favorable. That we do stand where we are today is of course thanks to a number of factors that are all equally important; the technological advancements that have led to our current state of the art devices; the dedicated scientists and physicians who possessed the vision and pursued the procedures to their present state of development; and not least the self-sacrifice of the brave individuals, like our ET patient, who agreed to volunteer and be test-subjects for these exciting and truly futuristic procedures.

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