Potential intracranial applications of magnetic resonance–guided focused ultrasound surgery

A review

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Magnetic resonance–guided focused ultrasound surgery (MRgFUS) has the potential to create a shift in the treatment paradigm of several intracranial disorders. High-resolution MRI guidance combined with an accurate method of delivering high doses of transcranial ultrasound energy to a discrete focal point has led to the exploration of noninvasive treatments for diseases traditionally treated by invasive surgical procedures. In this review, the authors examine the current intracranial applications under investigation and explore other potential uses for MRgFUS in the intracranial space based on their initial cadaveric studies.

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KEY WORDS • magnetic resonance–guided focused ultrasound surgery •
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THE combination of high-resolution MRI and improved focused ultrasound transducer technology has led to the emergence of the field of MRgFUS. The significant issues of focusing ultrasound beams through the intact human calvaria have largely been overcome. There is renewed enthusiasm from neurosurgeons to noninvasively treat targets and lesions deep within the brain and to avoid the potential side effects of ionizing radiation. In this review, we examine the current state of MRgFUS of intracranial disease and detail potential future directions.

Background

The potential benefits of using focused ultrasound energy to create lesions in the brain were recognized by Lars Leksell; however, limitations in quality imaging mo-

dalities and the need for a craniectomy window led him to investigate ionizing radiation, with the eventual creation of the Gamma Knife.²¹ More recently, Ram et al.⁴² used a craniectomy window to create thermal lesions in patients with brain tumors, but transducer technology has now advanced such that this step is no longer necessary. Phased array transducer technology allows the beams of ultrasound energy to be electrically steered in such a way that the defocusing effect of the human calvaria is obviated. In one such device, 1024 individual ultrasound elements are arranged in a hemispheric orientation to allow ultrasound energy to be focused on a central point in the brain (ExAblate Neuro, InSightec; Fig. 1). Hynynen et al.^{19,20} demonstrated the feasibility of treating intracranial lesions with animal models prior to the development and use of such systems in humans. McDannold et al.³⁴ then went on to successfully treat 3 patients with glioblastoma using real-time MRI thermometry feedback to ensure accurate targeting.

Abbreviations used in this paper: ICH = intracerebral hemorrhage; MRgFUS = magnetic resonance–guided focused ultrasound surgery; TCCD = transcranial color-coded duplex; TCD = transcranial Doppler; tPA = tissue plasminogen activator.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Fig. 1. The commercially available MRgFUS system combines a clinical 3-T MRI system with a transcranial hemispheric array transducer (650 kHz) that has 1024 ultrasound elements. The patient's head is fixed to the system in a stereotactic frame and the transducer is filled with degassed water to allow ultrasound waves to propagate toward the patient's head. A diaphragm placed around the patient's scalp keeps the water in place. Treatment planning is based on MRI, and MR thermometry is used for target verification during the sonication process. Routine MRI can be performed during and after the procedure to monitor treatment effect.

Current State of Clinical Applications

In 2009 Martin et al.³² were the first to use MRgFUS to treat patients with chronic neuropathic pain. Nine patients underwent selective medial thalamotomy. Lesions were created under real-time MRI guidance, and ablative areas of 4 mm in diameter were produced with peak temperatures of between 51°C and 60°C, as measured by real-time MRI thermometry. There were no significant treatment-related complications or side effects.³² Since these initial results, Elias et al. at the University of Virginia have begun an FDA-approved Phase 1 trial of MRgFUS in the treatment of essential tremor (WJ Elias et al., oral presentation, Annual Meeting of the Congress of Neurological Surgeons, Washington, DC, 2011). Other centers around the world are beginning to explore this technology for creating noninvasive lesions to alleviate the disabling symptoms of movement disorders. Stereotactic lesioning for movement disorders is an ideal application for transcranial MRgFUS because effective deep brain targets are accepted, and their volume of treatment is small, potentially requiring only a few sonications to achieve efficacy. Furthermore, the symptom relief can be clinically monitored during the treatment, and the treatment could be adjusted or suspended if side effects develop. Future clinical trials involving metastatic brain tumors, gliomas, and Parkinson disease are currently in the planning stages.

Sonothrombolysis

The use of ultrasound to enhance revascularization has been under investigation since the 1960s and 1970s.^{2,9,15,28,51,54} The mechanism of action is thought to be due to a combination of factors including heat generation, particle movement, and cavitation. With the use of high-

intensity focused ultrasound, temperature has not been proven to play a significant role.^{12,16,36} It is generally accepted that clot lysis depends on inertial cavitation, where microbubbles expand rapidly and collapse violently with the resultant mechanical force causing clot lysis.^{15,24,45–48} Lower-frequency systems (230-kHz ExAblate transducer) can use cavitation for treatment effect while mid-frequency (650-kHz) or high-frequency (1-MHz) systems are more ideal for creating a precise thermal lesion with the avoidance of cavitation.

Clinical use of ultrasound to augment the use of tPA has been widely used in the treatment of acute ischemic stroke. Tsivgoulis and associates⁵⁵ performed a meta-analysis of 6 randomized (224 patients) and 3 nonrandomized (192 patients) clinical trials. Some trials included the use of microspheres and there were 3 devices used including TCD, TCCD, and low-frequency ultrasound. Pooled results demonstrated that recanalization rates were higher in patients receiving TCD and tPA (37.2%) compared with tPA alone (17.2%). In the 8 trials of high-frequency (TCD/TCCD) ultrasound-enhanced thrombolysis, tPA plus TCD/TCCD was associated with a high rate of complete recanalization compared with tPA alone (OR 2.99, $p = 0.0001$).⁵⁵ The Transcranial Ultrasound in Clinical Sonothrombolysis (TUCSON) trial demonstrated the safety and efficacy of microsphere-potentiated sonothrombolysis in 35 patients. It showed that recanalization rates tended to be higher in the microsphere plus TCD groups (2 different doses of microspheres were used) and that recanalization occurred sooner. However, there was a higher rate of symptomatic ICH ($p = 0.028$) in patients receiving a higher dose of microspheres.

In the treatment of ICH and ischemic stroke, MRgFUS has potential to overcome the issues of a nonfocal ultrasound without the need for tPA. In the case of ICH, transcranial sonothrombolysis would be performed to accurately liquefy the ICH, thereby permitted MRI-guided aspiration of the liquefied clot through a small drainage tube in the same setting. Heating is minimal when duty cycles of 10%–20% are used without causing a decrease in lysis efficiency. After aspiration in the MRI/ultrasound suite, MRI is performed to confirm adequate liquid clot removal, and the drainage tube is removed. This minimally invasive approach has the potential to cause less disruption of normal brain tissue and to minimize the risks of meningitis and encephalitis resulting from leaving a drainage tube in the brain for prolonged periods. The safety and efficacy of the 230-kHz ExAblate phased-array transducer system has been demonstrated by our laboratory group and by others in both cadaveric and swine models of ICH (S Harnoff, oral presentation, Annual Conference for MRI Guided Focused Ultrasound Surgery, Washington, DC, 2008; SJ Monteith et al., electronic poster presentation, Annual Meeting of the Congress of Neurological Surgeons, Washington, DC, 2011; SJ Monteith et al., oral presentation, World ICH Conference, Newcastle upon Tyne, UK, 2011; and SJ Monteith et al., oral presentation, MR-Guided Focused Ultrasound Second International Symposium, Washington, DC, 2010). Such a setup could be used in the setting of ICH/intraventricular hemorrhage in infants, permitting early

and rapid evacuation of the blood clot. Such an intervention may decrease the rate of shunt dependence in these infants.

Epilepsy

For medically refractory epilepsy patients, resection can be very effective when the seizure focus can be identified. It is a safe and effective intervention when appropriate candidates are chosen for surgical intervention.⁵³ Non-invasive techniques involving stereotactic radiosurgery have shown promise for mesial temporal epilepsies, hypothalamic hamartomas, and corpus callosotomy.^{1,4,11,13,41} Concerns regarding the use of stereotactic radiosurgery in epilepsy involve the latency of the treatment effect and the potential risk of secondary malignancy due to ionizing radiation, which is very pertinent in a pediatric or young adult population. Transcranial MRgFUS could similarly treat many forms of epilepsy without craniotomy by lesioning of epileptogenic foci or by interrupting the fiber pathways involved in the propagation of epileptiform activity. It has the added benefit of permitting repeated treatments for a larger treatment volume without the fear of the cumulative radiation dose.

The concerns regarding the use of MRgFUS to treat epilepsy involve issues of inadvertent heating of the skull base and critical structures, such as cranial nerves, as a result of the “shadow” effect of energy distal to the focal point at the target. In our experience of using both a 230- and 650-kHz system in a cadaveric laboratory setup, these collateral heating effects can be minimized by creating no-pass regions over critical skull base structures such as the internal acoustic canal. Similar to blocking performed with radiosurgery devices, structures of concern can be selected out and highlighted on the planning MR image. The system software is able to turn off ultrasound beams that are directed through these areas, thereby preventing energy deposition and unwanted heating. Using such a setup, we have been successful in creating discrete thermal rises in fresh unpreserved cadaveric brains in the mesial temporal lobe, corpus callosum, and hypothalamic regions (Fig. 2). In the clinical setting, such increases in temperature would be performed to create a thermal lesion and ablate the tissue. While additional safety studies need to be performed, our initial experimental data suggest that MRgFUS may have a future role in the minimal-access ablation of subcortical epileptogenic foci. For now, cortical foci remain beyond the treatment envelope of focused ultrasound technology.

Septum Pellucidotomy, CSF Diversion, and Cyst Fenestration

Hydrocephalus is only amenable to neurosurgical intervention. Obstruction of CSF, resulting from a variety of etiologies, can occur at many different levels of the CNS axis and restoration of normal CSF dynamics is paramount for clinical success. Traditionally, shunting of trapped CSF has been the primary treatment, but there are occasions when alternative CSF diversion strategies are required, including endoscopic septum pellucidum

FIG. 2. **Left:** Treatment plan (software screen capture) and beam path of ultrasound waves directed at the hippocampal target in a cadaveric specimen. Each beam can be traced along its path to determine if certain beams should be disabled. Critical neuroanatomical structures can be protected by blocking ultrasound energy from being delivered along these paths. **Right:** A discrete temperature rise (9°C in this case) as measured by real-time MR thermometry at the target in this laboratory setup. Scattered signal in the lower third of the panel is indicative of a noise signal created by the bones of the skull base.

fenestration or third ventriculostomy. These methods are attractive options as they save patients from having to undergo placement of a shunt and the inherent ongoing issues associated with this therapy. Endoscopic third ventriculostomy has been shown to be a viable option for obstructive hydrocephalus^{18,49} in children who are older than 2 years.³ In addition, it has also been shown to be a possible treatment option for patients with hydrocephalus due to intracranial hemorrhage, but the procedure is technically demanding because of impaired visualization.³⁸

In this setting, MRgFUS is used to create a cavitation-induced lesion in neural tissue to permit the free flow of fluid (CSF) from one fluid compartment to another. MRgFUS third ventriculostomy, lamina terminalis fenestration, and/or septum pellucidotomy represent conditions in which a single, discrete lesion could alleviate hydrocephalus. In patients with loculated hydrocephalus, there are often several pockets of CSF that do not communicate, necessitating multiple fenestration surgeries or placement of multiple CSF shunts. With MRgFUS, multiple or contiguous lesions could be made in one noninvasive procedure. Most importantly, these treatments could be monitored with MRI for accuracy. Intraprocedural cine imaging studies could confirm the success of the treatment by demonstrating the restoration of CSF flow. The feasibility of targeting and treating the septum pellucidum (Fig. 3) and the floor of the third ventricle (Fig. 4) is illustrated in our cadaveric studies utilizing the 650-kHz cranial system.

Trigeminal Neuralgia

Trigeminal neuralgia is predominantly medically managed with carbamazepine, gabapentin, pregabalin, and baclofen. Patients in whom medical management fails will be referred to a neurosurgeon for surgical consideration. Microvascular decompression is the gold standard of surgical interventions and directly deals with the offending vascular structure impinging on the trigeminal nerve.^{22,52} Percutaneous techniques include glycerol injection, thermocoagulation, radiofrequency ablation, and

Fig. 3. Coronal (**left**) and axial (**right**) planning T2-weighted MR images demonstrating the target (small blue circle centered over the septum pellucidum) and beam paths of the ultrasound waves in a cadaveric laboratory setup. The green circle (right) indicates the treatment envelope that can be maneuvered by moving the transducer. Creation of a lesion in the septum pellucidum or the wall of a loculated enlarging CSF pocket may facilitate restoration of normal CSF hydrodynamics and prevent the need for invasive surgical procedures such as an endoscopic third ventriculostomy or a shunt placement.

balloon compression.^{6,8} Noninvasive treatment with stereotactic radiosurgery devices such as the Gamma Knife have demonstrated efficacy with pain relief rates similar to those of percutaneous techniques, but there is usually a delay in treatment effect of approximately 2 months. There is also a risk of radiation-induced injury to critical structures such as the pons. Complications such as anesthesia dolorosa and facial numbness may also occur, and these risks are increased in patients who undergo repeated treatment.^{17,27,29–31,37,40,43,44,50,56} Such radiation-related injury risks are not present with MRgFUS; however, the benefits of a noninvasive therapy without the need for general anesthesia remain.

After the successful use of the ExAblate Neuro system for thermal targeting and lesioning in the setting of brain tumors and functional applications in patients (WJ Elias et al., oral presentation, Annual Meeting of the Congress of Neurological Surgeons, Washington, DC, 2011),^{34,42} we examined a cadaveric feasibility targeting model of trigeminal neuralgia to determine if targeting of the trigeminal neuralgia with MRgFUS (650 kHz trans-

Fig. 4. Axial (**left**) and sagittal (**right**) planning images for MR-guided focused ultrasound third ventriculostomy in a cadaveric model. The small green-blue rectangle (right) delineates the target of the third ventricular floor. Rapid temperature drop-off and highly accurate MR-guided lesioning make MRgFUS an ideal tool for creating communication between CSF spaces and restoring normal CSF hydrodynamics. Cine MRI flow studies could be performed intraoperatively before and after the lesioning to monitor treatment effect.

ducer) was feasible. Targeting at the root entry zone and cisternal segment of the cadaveric trigeminal nerve was achieved with a mean temperature rise of 10°C (maximum 18°C) (Fig. 5). While there are limitations to using cadaveric models (large temperature rises are not possible, cavitation effects can occur due to tissue decay, and there is no CSF or blood circulation to assist in cooling of structures adjacent to target), these preliminary experiments demonstrate that focal heating of neuroanatomical structures of the skull base such as the trigeminal nerve is possible.

Due to concerns that the skull base will be heated by the so-called shadow of ultrasound waves distal to the target, thermometry experiments have been performed.³⁵ Thermocouple experiments with an in vitro skull demonstrated that, with appropriate application of no-pass regions over the petrous bone, heating of the internal acoustic canal could be decreased to 5.7°C.³⁵ With appropriate blocking of the internal acoustic canal, there was no significant thermal rise in the vicinity of other structures of interest including cranial nerves and cerebral vessels.³⁵ In vivo studies will need to be performed to determine the necessary focal temperature rise needed to achieve a therapeutic effect. In the case of radiofrequency ablation, temperatures in the range of 55°–70° are achieved.²³ It is likely that in the clinical setting for MRgFUS, a combination of real-time MR thermometry and clinical response in the awake

Fig. 5. **A–D:** The ultrasound beam paths can be traced in each plane toward the target (green spot on the T2-weighted planning MR images). Focal heating occurs at the root entry zone target, increasing by 18°C (D). The treatment envelope is overlaid as a large green circle. The green circle represents the planned treatment spot, while the cross-hair represents the natural focal point of the transducer (D). Targeting close to the natural focus of the transducer decreases the degree of electrical steering required and improves efficiency. The PRF (pulse repetition frequency) signal in the upper left of panel D is indicative of signal noise caused by bone. Reproduced with permission from Monteith et al: *J Neurosurg* [epub ahead of print November 16, 2012. DOI: 10.3171/2012.10.JNS12186].

patient would be used to determine when an appropriate thermal dose has been delivered to the target.

Anterior Cingulotomy and Psychosurgery

Lesioning of the anterior cingulate gyrus, or cingulotomy, can alleviate pain,^{14,57} severe depression, obsessive-compulsive disorder, and chronic anxiety.^{7,10,14} A noninvasive approach that involves stereotactic radiosurgery is also possible, but there are risks associated with the delivery of radiation.²⁵ Transcranial MRgFUS could similarly be used for cingulotomy procedures, as multiple lesions could be delivered while the patient is monitored clinically. Simulation experiments performed by our group at the University of Virginia have demonstrated that the cingulate gyrus is within the theoretical treatment envelope for both the 650- and 230-kHz ExAblate Neuro systems (Fig. 6). The lower range system may be more appropriate for this procedure because its range is less limited, and its sonication diameters are larger. Pilot clinical trials involving MRgFUS in the setting of psychiatric disease are in the planning stages.

FIG. 6. Laboratory simulation of MR-guided focused ultrasound anterior cingulotomy using MR thermometry and an explanted human calvaria. The sagittal MR images show the target. A thermosensitive gel molded to the inside of the skull is targeted. The cross-hair and rectangle target in the large panel demonstrates accurate targeting. A discrete temperature rise is seen at the target using real-time MR thermometry. **Inset:** A real-time MR thermometry graph demonstrates a discrete temperature rise at the focal point over time to a maximum temperature increase of 8°C from baseline (graph is calibrated to a 37°C baseline).

Targeted Drug Delivery

Drug delivery to the CNS is limited by the blood-brain barrier. Few systemic drugs cross this protective structure to achieve therapeutic concentrations regardless of disease. Multiple strategies have been investigated to open the blood-brain barrier to permit the release of therapeutic compounds. It has been demonstrated in the laboratory that focused ultrasound can achieve precise and transient opening of the blood-brain barrier. The mechanism utilizes pulsed, nonthermal ultrasound waves to create a sustained (and not inertial) cavitation.^{33,39}

The ideal drug is one that acts upon its target without having any effect on remaining tissues. At times this is not feasible, particularly in the setting of CNS disease in which the specificity of drugs used in the treatment of tumors is not as high as would be ideal. Targeted drug delivery relies on the use of pulsed ultrasound energy to reversibly open the blood-brain barrier, thereby allowing systemically administered drugs to be delivered in higher concentrations to target tissues. Preclinical studies have demonstrated that it is possible to deliver drugs in higher concentrations to regions of the brain using targeted drug delivery in animals; however, MRgFUS-targeted drug delivery use in patients with CNS tumors is not yet at the clinical trial stage.^{5,26}

Limitations

The limitations of transcranial MRgFUS include the range and volume of intracranial treatments, time, and cost. Due to physical limitations imposed by the skull, it is not currently possible to focus the ultrasound beams adjacent to the convexity; thus, central targets are more favorable. Treatment times may be lengthy due to the need for ongoing MRI during the procedure, either for target confirmation or thermal measurements. The treatment of tumors with thermal lesioning may be time consuming if multiple sonications are required for a large-volume tumor. Controlled cavitation may allow for larger lesions and shorter treatment times, although the safety of this approach needs to be addressed and only recently have protective cavitation detectors been implemented into clinical systems. Finally, current MRgFUS systems are expensive, and there are no regulatory-approved clinical applications for brain disorders. The setup cost for such a system involves the purchase of a 3-T clinical-grade MRI scanner as well as the MRI-compatible ultrasound transducer for brain targeting.

Conclusions

Magnetic resonance-guided focused ultrasound surgery is a developing subspecialty of neurosurgery. Advanced phased-array transducer technology obviates the need for a craniectomy window. Coupled with the continual improvement in MRI equipment, there is potential to treat deep targets within the brain for various CNS conditions. It is possible that several neurosurgical diseases currently treated routinely with open surgery will soon be referred to the MRgFUS suite for noninvasive, nonionizing brain surgery.

Disclosure

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