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Cavitation-based third ventriculostomy using MRI-guided focused ultrasound:

Laboratory investigation

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Abstract

Object—Transcranial focused ultrasound is increasingly being investigated as a minimally invasive treatment for a range of intracranial pathologies. At higher peak rarefaction pressures than those used for thermal ablation, focused ultrasound can initiate inertial cavitation and create holes in the brain by fractionation of the tissue elements. The authors investigated the technical feasibility of using MRI-guided focused ultrasound to perform a third ventriculostomy as a possible noninvasive alternative to endoscopic third ventriculostomy for hydrocephalus.

Methods—A craniectomy was performed in male pigs weighing 13–19 kg to expose the supratentorial brain, leaving the dura mater intact. Seven pigs were treated through the craniectomy, while 2 pigs were treated through ex vivo human skulls placed in the beam path. Registration and targeting was done using T2-weighted MRI sequences. For transcranial treatments a CT scan was used to correct the beam from aberrations due to the skull and maintain a small, high-intensity focus. Sonications were performed at both 650 kHz and 230 kHz at a range of intensities, and the in situ pressures were estimated both from simulations and experimental data to establish a threshold for tissue fractionation in the brain.

Results—In craniectomized animals at 650 kHz, a peak pressure 22.7 MPa for 1 second was needed to reliably create a ventriculostomy. Transcranially at this frequency the ExAblate 4000 was unable to generate the required intensity to fractionate tissue, although cavitation was

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initiated. At 230 kHz, ventriculostomy was successful through the skull with a peak pressure of 8.8 MPa.

Conclusions—This is the first study to suggest that it is possible to perform a completely noninvasive third ventriculostomy using ultrasound. This may pave the way for future studies and eventually provide an alternative means for the creation of CSF communications in the brain, including perforation of the septum pellucidum or intraventricular membranes.

Keywords

focused ultrasound; MRIGFUS; minimally invasive surgery; third ventriculostomy; high-intensity focused ultrasound; hydrocephalus; pig

Treatment options for hydrocephalus include CSF shunting procedures or endoscopic third ventriculostomy (ETV). In the developed world, ETV is often the preferred treatment for obstructive hydrocephalus as it avoids shunt dependency and the need for permanently implanted hardware.⁶ In the developing world, ETV is even more desirable, given the barriers to accessing timely and competent neurosurgical care in the event of shunt malfunction or infection. Endoscopic third ventriculostomy is not without risk, however, with morbidity and mortality reported in the range of 10%–15%.⁶ Furthermore, not all patients are suitable candidates, and as many as 30% of ETVs may be aborted due to distorted anatomy or poor visibility.³⁵ The creation of a ventriculostomy under MRI guidance could potentially alleviate the difficulties of highly distorted surgical anatomy and poor visibility, and possibly improve safety in those cases in which direct visualization is not possible. To this end, we investigated the feasibility of pairing focused ultrasound, a minimally invasive therapeutic modality capable of tissue fractionation, with MRI guidance (together referred to as MRIGFUS), to tunnel through the floor of the third ventricle using inertial cavitation.

The bioeffects of ultrasound can be categorized as thermal or nonthermal. As ultrasound waves propagate through tissue, energy is absorbed, resulting in temperature elevation. This has been well studied and can be exploited to create focal heating resulting in protein denaturation and cell death.²⁹ It has also been shown that focused ultrasound can be used to disintegrate tissue such that holes or tunnels are created.^{13,18,19,32,38,39} To rapidly perforate or fractionate tissue, however, inertial cavitation is required as thermal mechanisms leave the tissue—at least acutely—structurally intact. Acoustic cavitation refers generally to the interaction of sound waves with gas bodies in a liquid medium. Small cavitation nuclei (microbubbles) may exist in tissues, while gas or vapor voids may be generated by ultrasound waves of sufficiently high peak rarefaction pressures. In such an ultrasound field, these gas bodies oscillate, expand by rectified diffusion toward a resonant volume, and violently collapse, resulting in high temperatures, shock wave formation, and fluid jets.²⁴ The resulting effects in the brain due to cavitation are distinct from those caused by thermal mechanisms and are characterized by the complete destruction of ultrastructural tissue elements and the formation of cavities.^{3,8,33,34}

To generate the conditions necessary for cavitation, high-intensity ultrasound beams are needed. While early researchers were able to generate lesions in the brain using cavitation,

craniotomies were required to prevent significant attenuation and aberration of the focus due to ultrasound propagation through the skull. Furthermore, skull heating could result in burns to the scalp as well as to the adjacent intracranial contents. Over the past 2 decades, transmission of ultrasound through the intact skull has been made possible using large, high-power hemispherical phased array transducers.¹⁶ In this way, the energy absorbed by the skull is distributed over a larger area, while the scalp can be cooled by a water bath simultaneously used to couple the transducer to the patient. To achieve a small focal region suitable for neurosurgical applications, CT images of the skull are used to calculate, for each of the elements of the array, the phase difference acquired upon transmission through the skull, thus allowing the ultrasound wave from each element to converge at the focus in-phase and thus add constructively to obtain the maximum intensity.⁴ A similar technique, performed in the MRI environment with structural imaging and real-time thermometry, has been successfully used in Phase I clinical trials for the creation of highly localized thermal lesions in the brain.^{20,22}

Therapeutic ultrasound used in early clinical studies has intentionally remained below the cavitation threshold and relied solely on thermal lesion formation. We investigated the feasibility of performing third ventriculostomy in swine by the deliberate inception of inertial cavitation using a commercially available clinical ultrasound system (ExAblate 4000, InSightec).

Methods

Craniectomy

All procedures were approved by the institutional animal care and use committee. General anesthesia was induced in male pigs weighing 13–19 kg with isoflurane followed immediately by endotracheal intubation and mechanical ventilation. Intravenous access was established to allow for intraoperative fluids and analgesia (buprenorphine 3 µg/kg), and pulse oximetry was used to monitor heart rate and blood oxygen saturation. Animals were positioned prone, and the scalp hair was removed with clippers followed by chemical depilation in preparation for subsequent focused ultrasound treatments. A U-shaped incision was marked and subcutaneously injected with epinephrine (dilution 1:100,000) to minimize blood loss. A wide craniectomy was performed, exposing the intact dura from the frontal air sinuses to the posterior fossa in the anteroposterior direction, and laterally to the cranial base. The orbits were unroofed to give as much an unobstructed path as possible for the ultrasound beam. The margins of the craniectomy were waxed for hemostasis. The scalp was then reapproximated with sutures. The surgical cavity was irrigated with 0.9% saline via a small length of intravenous tubing inserted through the incision to flush any air bubbles from under the scalp that would otherwise support cavitation away from the intended targets. Postoperatively, animals were kept under general anesthesia and were moved to the MRI suite for focused ultrasound.

MRigFUS

Treatments were performed using a clinical MRigFUS system (Exablate 4000, InSightec) combined with a 3-T MR scanner (Signa MR750, GE Healthcare). Normothermia was

maintained with a warming blanket, and animals were administered warmed maintenance intravenous fluids during the treatment. The animals were secured to the treatment table with straps across the head and torso. The hemispherical array was then carefully filled with degassed water. T2-weighted MRI sequences were performed in 3 orthogonal planes for coregistration of the MRI and ultrasound coordinate systems and were subsequently used for targeting (FSE-XL, FOV 160 mm, 256×192 matrix, slice thickness and spacing 2 mm, TR 3000 msec, TE 71.3 msec). The ExAblate treatment planning software, operated in research mode, was then used to select the sites for sonication. Prior to beginning high-power sonications, the focal spot location was confirmed by performing a low-power sonication to induce a mild temperature elevation, measured by MRI thermometry, at the presumed focus (Fig. 1A). Any minor misalignments were corrected at this time prior to beginning treatments. The focal spot size was $2.1 \text{ mm} \times 1.05 \text{ mm}$ for the 650-kHz treatments and $5.8 \text{ mm} \times 3.0 \text{ mm}$ for the 230-kHz system (calculated axial and lateral intensity full-width-at-half-maximum, respectively). While the software was not designed to perform sonications consisting of short pulses, this was made possible by externally triggering the ExAblate with a function generator. Treatment parameters are detailed in Table 1. During the treatments, acoustic emissions were recorded using 2 hydrophones installed within the array (Fig. 2; 5-MHz sampling for 15 msec of each 100-msec epoch for the duration of the treatment). Strong half-harmonic and broadband emissions were used to confirm the presence of inertial cavitation (Fig. 2B).^{14,25,34} Posttreatment imaging was performed in 3 orthogonal planes.

Transcranial Treatments

Two animals were treated through an ex vivo human calvaria (Fig. 1B and 1C): one with the 650-kHz system and the other with the 230-kHz system. The ex vivo calvaria was completely submerged in deionized water and degassed for 24 hours prior to focused ultrasound treatments. Previously obtained CT images of the calvaria were loaded into the InSightec treatment planning software and were manually aligned with the MR images for phase correction.

In Situ Pressure Estimation

The ExAblate 4000 allows electronic steering of the focus within a predefined volume centered on the geometrical focus. Although the heads of the animals were positioned so that the floor of the third ventricle was as close to the geometrical focus as possible, they did not correspond exactly, and thus electronic steering was required for accurate targeting. This resulted in a reduced intensity at the targets, compared with the maximum intensity without steering, for a given input power. To estimate the effect of steering on the treatments, InSightec provided intensity measurements taken at 5-mm steering intervals along 3 orthogonal axes. The reduction in intensity with steering was nearly spherically symmetric about the peak (x, y, and +z direction; steering to a point closer to the array generated a slightly higher intensity compared with the farther point equidistant from the focus; however, due to anatomical constraints of positioning, the target was never found within this region), and thus this approximation was used to generate a scaling factor for the input power for each treatment. Magnetic resonance imaging coordinates of both the focus and the target location were used to calculate the distance steered and generate the scaling factor for each target. This generated an error that we estimate was at most 10%.

The pressure transmission coefficient through the ex vivo calvaria at 230 kHz was calculated from the average of the measured relative decrease in pressure amplitude due to the introduction of the skull compared with the free field pressure in water. The relative pressure amplitude due to a 1-W, 1-msec burst was measured using a 0.5-mm needle hydrophone (Precision Acoustics) positioned at the geometrical focus of the array and recorded with an oscilloscope (WavePro 715Zi, Teledyne LeCroy) consecutively for each of the array's 1024 elements, both with and without the human calvaria in place. After envelope detection, the signal was averaged over a 0.5-msec epoch once the recorded signal had stabilized in amplitude.

The in situ pressure was estimated using several different techniques, neglecting nonlinear effects. The physical brain tissue properties used are summarized in Table 2. As an upper limit, the peak pressures were simulated with Matlab (Mathworks) using an element size and geometry provided from InSightec. As an estimate for the 650-kHz system, the peak pressure was estimated from data recorded from previous thermal lesioning experiments using Equation 1. Using a plane wave approximation at the focus and noting that the time-averaged rate of heating per unit volume, $\bar{q}$, is related to the derivative of the time-averaged intensity, $\bar{I}$, with respect to z , the pressure can be derived from Equation 2.^{16,26}

$$\bar{q} = -\frac{d\bar{I}}{dz} = 2\alpha_a \bar{I} = C_m \rho_b \frac{\Delta T}{\Delta t} \quad [\text{Eq. 1}]$$

$$|p| = \sqrt{2\rho_b C_b \bar{I}} = \sqrt{\frac{C_m \rho_b^2 C_b \frac{\Delta T}{\Delta t}}{\alpha_a}} \quad [\text{Eq. 2}]$$

The rate of temperature change was calculated from the average temperature increase in 9 voxels (27 mm³) recorded by MR thermometry over the first sampling interval (3.7 seconds) of a 20-second sonication. As a result of the short time interval, thermal conduction and perfusion effects were neglected in this approximation. The temperature distribution was modeled by a 3D gaussian proportional to the calculated intensity field for the hemispherical array. Corrections were made to Equation 2 for beam steering and both skull and brain attenuation, and this is reflected in the estimated error in Table 1. The power transmission coefficient for human skull was estimated from published data to be 20% for incidence angles of $\pm 10^\circ$.^{7,37} Finally, for the 230-kHz system, we used calibration data from the literature and corrected it for spatial averaging over the 4-mm hydrophone to give an estimate of the peak pressure.²¹

Histological Examination

Animals were euthanized by intravenous injection of Euthanyl while under general anesthesia. The incisions were then reopened and the brains were carefully removed. The cranial nerves and skull base were examined for evidence of tissue damage. The brains were fixed in 10% neutral buffered formalin for 1 week, examined for any sign of a lesion or tissue injury, and cut in 5-mm coronal sections. These gross sections were digitally photographed prior to routine tissue processing and paraffin embedding. Histological

sections were then cut at 1-mm levels and stained for H & E. These were then digitized using a TISSUEScope scanner (Huron Technologies) for analysis.

Statistical Analysis

All measured values are reported as mean $\pm$ SD. The Pearson product-moment correlation coefficient was calculated to measure the correlation between treatment effects and peak pressure.

Results

A third ventriculostomy was performed successfully in 6 of 9 animals, confirmed by both gross and microscopic examination. Animals tolerated both the surgical and ultrasound procedures without incident. The treatment parameters resulting in successful ventriculostomy are summarized in Table 1.

Treatment Monitoring and Imaging

Identification of a successful ventriculostomy by MRI during the treatment was difficult because of the use of the body coil, as a head coil would have required removing the animal from the treatment fixture. Mechanical ventilation–related motion also sometimes degraded the image quality. On the T2-weighted sequences, a ventriculostomy was often visible due to the presence of a low-intensity signal in the region of the third ventricle floor, attributable to blood products. On posttreatment MRI, performed with a head coil once the animal was removed from the treatment fixture, we were able to detect the lesion in all cases, and the maximum axial dimension was in good agreement with that measured on the H & E–stained histology sections (Fig. 3; Table 1). In one animal in which no blood was found at the focus on histology, the ventriculostomy was more difficult to appreciate. Cerebrospinal fluid flow imaging was attempted unsuccessfully in one animal; we were unable to capture the animal's heart rate adequately with surface electrodes. No collateral parenchymal injury was seen in any of the animals.

The temperature at the focus was monitored continuously during the treatments by MR thermometry and did not show a significant increase in temperature. Significant heating was not detected in soft tissues adjacent to the skull base during the treatment, which would have indicated in the present model that the floor of the third ventricle was too close to the skull base to be safely perforated with focused ultrasound. In all treatments, strong half-harmonic and broadband emissions were detected by the system's built-in hydrophones, confirming the occurrence of inertial cavitation (Fig. 2B and C).^{14,25,34}

Histological Examination

Gross examination of the skull base, including the pituitary gland and nearby cranial nerves, did not reveal any obvious abnormalities. In successful treatments at both frequencies, a small amount of subarachnoid hemorrhage was often seen in the vicinity of the third ventriculostomy (Fig. 4). In 5 of 6 successful ventriculostomies, a small amount of blood was seen at the newly created opening. This did not appear to be obstructive in nature. On gross examination of the entire brain, and subsequently the 5-mm coronal slices, there were

regions of petechial hemorrhage seen within the ultrasound path (Fig. 5A). Some test sonications were performed in the subcortical regions of the brain prior to the ventriculostomy in many of the animals, and therefore it was difficult to definitively separate these from an intentional lesion in all cases. However, particularly in the animal treated transcranially at 650 kHz, there was microhemorrhage identified distant to the sonicated regions. The morphology of the ventriculostomies was consistent with the ellipsoid focal shape, with the long axis in the superior-inferior orientation due to the position of the animal's brain relative to the array. Because the sonications were centered on the floor of the ventricle, the ventriculostomies are widest at the base of the brain with the hemispheres extending upward into the third ventricle (and brain in the case of the pig), and downward into the subarachnoid space.

Microscopic histological examination of the ventriculostomies revealed very sharply demarcated regions of tissue destruction, with a central void surrounded by a thin rim of abnormal-appearing tissue that ranged between 0.4 mm and 0.9 mm (0.65 ± 0.16 mm). The contour of the cavity was slightly more irregular appearing in the ventriculostomy created at 230 kHz (Fig. 5). Beyond this rim, hemorrhage was seen to surround some small vessels in the vicinity, extending 0.4–1.5 mm (0.9 ± 0.4 mm) from the cavity's edge in the 650-kHz treatments, and extended up to 3.2 mm at 230 kHz. A minority of vessels within this range were affected. In some animals microhemorrhages were identified distant to the focal region (Fig. 5A and B). These regions were typically identified within the white matter near the gray-white matter interface and were lenticular in morphology, with the long axis parallel to the orientation of the white matter fiber tracts. As stated previously, these were most noticeable in the animal treated through the human skull at 650 kHz. While ventriculostomy was unsuccessful in this animal, several sonications were attempted, in addition to a longer sonication at the floor of the third ventricle, which could have contributed.

Pressure Estimation and Cavitation Threshold

The power transmission through the human skull was 36% at 230 kHz and was estimated to be 20% at 650 kHz. For analysis, acoustic powers measured by the system were corrected for steering and, if applicable, the presence of a human calvaria, then converted to estimated peak pressures. Real-time estimations of the peak pressure at the focus were not available, and therefore all of the sonications with a pulse length less than 1 second were at the lower end of peak pressures obtained. Only one of these sonications resulted in a ventriculostomy and, as expected, was the smallest measured. All but one animal was treated at 650 kHz. Although cavitation was detected in all animals during the treatment, the pressure threshold for reliably causing tissue fractionation at the focus was 21.3 MPa (estimated range 21.3–37.3 MPa). Above this pressure the size of the ventriculostomy, measured in the axial plane, was seen to weakly correlate with increasing pressure ($r = 0.69$). However, the rim of tissue damage surrounding the ventriculostomy did not, and appeared to remain relatively constant in thickness regardless of the size of the lesion ($r = -0.22$; Fig. 6).

At 230 kHz, ventriculostomy was successfully achieved when an ex vivo human skull was inserted into the beam path, with an estimated in situ peak pressure of 8.7 MPa. Test sonications at other locations in the brain, at pressures up to 8.3 MPa, did not result in tissue

fractionation but did result in significant erythrocyte extravasation at the focus, consistent with the subthreshold sonications at 650 kHz. Transcranial ventriculostomy was unsuccessful at 650 kHz. A total of 3 sonications were performed without evidence of tissue fractionation, even when the pulse duration was increased. There were signs of cavitation within the brain, characterized by regions of erythrocyte extravasation surrounding the microvasculature, typically on the order of 200–300 μ m in diameter, and typically at gray-white matter interfaces away from the focus (Fig. 5).

Discussion

Magnetic resonance imaging–guided focused ultrasound for the treatment of hydrocephalus has potential advantages over existing therapies by avoiding implanted hardware, reducing the risk of infection, and shortening hospital stay due to its noninvasiveness. To date, MRigFUS has been used exclusively for thermal lesioning in the brain, albeit for a handful of applications.^{20,22} While ultrasound could be used to thermocoagulate the floor of the third ventricle, this would require a longer sonication, which may result in excessive heating of the skull base and to injury of adjacent neural and vascular structures.³⁰ Furthermore, while thermal lesions in the thalamus evolve over weeks to appear as fluid-filled cavities on follow-up MRI,²⁰ there is no guarantee that thermal lesions in the floor of the third ventricle would undergo the necessary tissue reorganization to result in an opening. As such, we investigated the use of inertial cavitation to create the required opening. The first results of third ventriculostomy with MRigFUS were presented by our group in early 2012 (Alkins et al., oral presentation, American Institute of Ultrasound in Medicine 2012 Annual Convention, Phoenix, AZ; Alkins et al., electronic poster presentation, American Association of Neurological Surgeons 80th Annual Scientific Meeting, Miami, FL). The only other mention is a 2013 review paper that suggests the possibility of the procedure in cadaveric heads but provides no results of, or references to, any experimental work.²³ In the past, cavitation was generally considered a mechanism to avoid in the brain as lesions were often associated with hemorrhage. More recently, investigators have safely harnessed cavitation to perform extracranial “histotripsy,” or the fractionation of tissue, for pathology involving cardiac,^{1,28,32,38,39} prostate,^{13,19} and fetal tissue.¹⁸

In the present study, we first showed that in crani-ectomized animals a highly localized opening could be generated in the floor of the third ventricle with a commercially available MRigFUS system, without causing significant damage to surrounding structures. We then attempted to perform the same intervention through an ex vivo human skull to approximate whether this could be performed in a human within the system's limitations. Transcranial MRigFUS ventriculostomy was successful only with the 230-kHz system due to the inverse relationship between frequency and both cavitation threshold and attenuation. The rim of the ventriculostomy at the lower frequency was more jagged appearing than that at the higher frequency, which we postulate may be attributable to the larger resonant bubble size at 230 kHz and thus perhaps more violent cavitation. While cavitation was detected in all treatments, the threshold “dose” to generate tissue fractionation is higher than that required to generate cavitation. Except in one animal, short bursts did not generate a ventriculostomy with the pressures achieved. It has been established previously that the cavitation threshold decreases with pulse duration, so this perhaps is not surprising.⁸ The cavitation threshold is

also expected to increase with frequency as predicted by theory,¹⁰ and this has been verified in vivo where it was found to increase linearly in muscle tissue.¹⁴ The present results are remarkably consistent with this relationship, where the ratio of the threshold pressures is almost identical to the ratio of the frequencies used (230 kHz/650 kHz $\approx$ 8.8 MPa/21.3 MPa). The size of the ventriculostomy at 230 kHz also most closely agrees with lower range of the openings created at 650 kHz, suggesting that 8 MPa was near the threshold. This is further supported by the fact that sonications at 230 kHz at peak pressures of 7.7 MPa did not result in tissue fractionation. Further validating our findings, the intensities that were used in the present study are also consistent with the range of intensities reported in the literature at which cavitation lesions were seen in the brain (10^3 – 10^4 W/cm²).^{8,33,34}

Safety of the Treatment

An important aspect of the present treatment is its safety. There was a small amount of clot at the ventriculostomy site in 5 of 6 cases, but this did not appear to be obstructive and was restricted to the immediate vicinity of the opening, suggesting that the bleeding resolved quickly. These fragments of clot were on the order of hundreds of microns in size (Fig. 6). The combination of one sonication to initially heat the target tissue and thermo-coagulate the vessels, followed by another to fractionate the tissue with cavitation, might reduce the amount of clot seen at the target site but was not performed during the present study. The ventriculostomies were highly circumscribed, with collateral damage seen at most 3 mm from the rim, and consisting in that case of only mild erythrocyte extravasation. Even in normal nonhydrocephalic humans, the width of the third ventricle is 5–6 mm,¹² so with accurate targeting, the only non-CSF element within this volume would be the intended target tissue. Because the focus is ellipsoidal, in humans the sonication could be centered slightly above the floor of the third ventricle to avoid any possibility of injury to structures below, such as the basilar artery. While there are no studies in the literature specifically investigating these high ultrasound pressures on large intracranial vessels, there are studies showing the effects of high intensities on the rodent (rabbit and rat) femoral artery.^{15,17} These studies were performed at higher frequencies (1.49 and 3.2 MHz) where the cavitation threshold would be much higher than that in the present study, so that the events described would occur at a lower intensity with the present experimental setup. These studies found that at intensities of 10^3 W/cm², spasm of the vessel occurred with a reduction in flow and occasional vessel occlusion, while at still higher intensities approaching 10^4 W/cm², spasm was seen, with occlusion, delayed necrosis, and in 25% acute vessel perforation.^{15,17} The high peak pressures used in the present study would almost certainly result in severe complications if superimposed on nontarget cerebral vessels, and should thus be avoided at all costs. Even in the confined space of the porcine circle of Willis, there was no injury to the basilar or posterior communicating arteries in the present study; the only injury visible on the base of the brain and outside the ventriculostomy was a highly localized and faint rim of subarachnoid hemorrhage.

In some animals there were regions of erythrocyte extravasation seen at gray-white interfaces distant from the focus. Grossly these could be characterized as micro-hemorrhage restricted to submillimeter regions. Previous studies have found that hemorrhage can occur at tissue interfaces, including at vessel or ventricular walls.³³ While we did not find any off-

target effects in the vicinity of the ventricles, the microhemorrhage described above was always centered on a vessel without any other signs of ultrasound-related damage (that is, vacuolation), suggesting that the event was vessel centric. It has been hypothesized that during multiple sonications, these hemorrhages could be attributed to gas nuclei that are generated during initial sonications and subsequently result in cavitation within the beam path.⁹ As we did perform test sonications prior to the ventriculostomy in the present study, this certainly could have contributed to the development of these regions of erythrocyte extravasation. There were no other discreet lesions noted due to the treatments. It has been previously shown that some lesions are not visible until 10–15 minutes after a sonication; the animals were killed beyond this time point, and therefore all structural lesions should have been identifiable.²

Treatment Monitoring

At the present time and with the current instrumentation, the only means of guiding the sonications was by stereotaxy and by ensuring that the low-intensity focal heating on thermometry sequences corresponded to the MRI coordinates used for successive high-intensity sonications. Beyond this, the hydrophone recordings served only to verify the presence of cavitation, but not its position. The amplitudes of the subharmonic emissions in the present study are unlikely to provide any additional information due to slight variations between successive animals, and the bandwidth of the hydrophone and filtering of the signal precluded absolute amplitude measurements. Although there is no defined measure of the “amount” of cavitation, it is conceivable that acoustic emissions could be used to quantitatively assess the cavitation events and thus guide the treatment, as is done with blood-brain barrier disruption.^{5,27} Cavitation mapping with an array of hydrophones might in the future allow confirmation of cavitation at the precise anatomical target. This could also be used to terminate sonications if cavitation was detected away from the focus. Given these limitations in monitoring, it is possible that in the unsuccessful cases in the present study, we simply missed the floor of the third ventricle and that cavitation occurred in the subarachnoid space. It has also been reported that there can be variations in the position of periventricular structures due to CSF pulsations.³¹ The largest dimension of the focus is orthogonal to the third ventricular floor, and hence parallel to its motion during CSF pulsations. If centered on the floor, the focal region would overlap the floor during even its largest excursions.³¹ While in the present study we were unsuccessful in establishing cardiac gating, in the future it might be possible to gate the sonications with the cardiac cycle or CSF pulsations, which might further be optimized using repeated short pulses as we found successful in one case, rather than a single 1-second sonication. In any case, prior to applications of this procedure in humans, further advances in cavitation detection and monitoring, and further optimization of the MRI sequences, are needed.

Study Limitations

While we have shown that MRigFUS third ventriculostomy is possible and appears safe in swine, there are a number of limitations with the present model. The morphology of the porcine skull is quite unlike a human calvaria. As a result, a hemispherical array, which is well suited for the relatively convex human calvaria, orients many of the array elements at an oblique rather than normal incidence to the skull, contributing to reflections and thus a

reduced transmitted intensity. For this reason, animals were craniectomized, which increases the risk of injury to the brain prior to the ultrasound procedure, prolongs the duration of anesthesia, and makes survival studies in this model less desirable. An additional anatomical difficulty was the small size of the third ventricle in non-hydrocephalic animals. The third ventricle was typically less than 1 mm wide and was difficult to visualize on the interprocedural MRI. As a result, some of the treatment failures may have been due to improper targeting. Also, nontarget tissue was encompassed within the focal region, but this would not be the case in humans. However, the third ventricle in humans is much larger, and the ExAblate system has been used successfully in conjunction with the 3-T MRI body coil to create lesions in the brain with 1-mm accuracy.²⁰ Finally, because the present study is not a survival study, we have no information on the durability of this procedure. The optimal model for this procedure might be a primate hydrocephalus model, where the skull shape is more similar to that of a human, and craniectomy is not required so that the patency of the ventriculostomy could be evaluated over the long term.

Conclusions

We have shown for the first time that MRigFUS ventriculostomy is feasible in live animal subjects with an available clinical transcranial ultrasound system. Further studies are needed to better assess the safety of the procedure, and these may best be performed in a hydrocephalic primate model. This is a preliminary study, and much optimization is needed before this technique can be translated to humans. Improved monitoring is needed, including cavitation mapping, which could improve the efficacy and safety of the procedure, while CSF flow MRI could be used to confirm flow through the opening. Focused ultrasound may eventually become an additional tool in the treatment of hydrocephalus, allowing the creation of not only of third ventriculostomies, but the perforation of the septum pellucidum or pathological intraventricular membranes.

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Abbreviations used in this paper

ETV	endoscopic third ventriculostomy
MRIgFUS	MRI-guided focused ultrasound

Fig. 1.

A: A sagittal MRI localizer obtained in the animal after positioning in the in-house fabricated fixture and 30-cm, 1024-element treatment array. The third ventricle floor was positioned as close as possible to the geometrical focus. **B:** The temperature elevation as measured by MR thermometry, processed by the InSightec treatment software. Prior to starting treatment sonications, the focal position was verified by sonicating at a low power to slightly heat the ultrasound focus and match the focus to that in the MR space. **C:** The degassed ex vivo human skull is shown secured horizontally to an in-house manufactured polycarbonate holder. The ExAblate 4000 hemispherical array was removed from its usual mount, positioned horizontally on a custom bed, and filled with degassed water prior to animal positioning.

Fig. 2.

A: The position of the 2 hydrophones is highlighted within the treatment array by the *dashed circles*. These were used to record acoustic emissions during all treatments. **B:** The acoustic emissions recorded during the third ventriculostomy with the 230-kHz system are displayed, with strong half-harmonic and broadband emissions. The presence of broadband emissions confirms the presence of inertial cavitation during the treatment. **C:** The temporal resolution of the cavitation detection system during a pulsed sonication was sufficient to capture the pulses. Three consecutive 300-msec pulses (pulse repetition frequency = 1 second) are seen to produce strong half-harmonic emissions in this unsuccessful treatment. Broadband emissions were also detected but at lower amplitudes.

Fig. 3.

Assessment of the treatment effects by T2-weighted MRI using an 8-channel head coil. **A:** Axial MR image showing the successful transcranial third ventriculostomy performed with the 230-kHz ExAblate system. The sonicated region is identified by the *arrow* in each plane. There is a rim of low signal intensity around the ventriculostomy, likely due to a small amount of fresh clot, improving visualization of the cavity. The *scale bars* are incremented every 1 cm. **B:** Coronal image through the ventriculostomy. **C:** Sagittal view through the ventriculostomy.

Fig. 4.

Gross sections of the treated brains with the 650-kHz system. **A:** The resultant ventriculostomy obtained with a peak rarefaction pressure of 15.7 MPa and 100-msec continuous sonication, measuring just over 2 mm. A small amount of clot can be seen at the site. **B:** The same lesion after cutting of the brain into 5-mm coronal slices. The blood from panel A can be seen in the third ventricle. **C:** The much larger ventriculostomy generated with a peak rarefaction pressure of 28.8 MPa for 1 second. The ventriculostomy is almost 9 mm in cross-sectional diameter and is free of any debris. **D:** The corresponding coronal view depicts the empty, smooth-walled cavity.

Fig. 5.

A: Off-target tissue injury is highlighted by the *dashed circles* in both hemispheres. Microhemorrhages can be seen at the superficial interface of the gray and subcortical white matter. **B:** The lumens of the damaged vessels can be identified in the centers of the microhemorrhages. This tissue damage identified in the near field is thought to result from multiple high-power sonications, where cavitation nuclei are generated within the near field on previous sonications.

Fig. 6.

Histological sections of the successful ventriculostomies. **A:** The large ventriculostomy generated with the 650-kHz ExAblate system shown in Fig. 4C and D. There is very fine tissue fractionation and a very sharply demarcated wall. **B:** In the magnified view, a few small vessels are seen adjacent to the ventriculostomy with extravasated erythrocytes. These occur not more than 1.5 mm from the rim of the cavity. **C:** The ventriculostomy performed with the 230-kHz system has a significantly different appearance. The tissue fractionation is coarser, with more hemorrhage and larger tissue fragments seen within the cavity. **D:** In the magnified view, there is a more obvious rim (< 1 mm) of pale tissue around the cavity. Vascular injury was noted up to 3.2 mm from the cavity wall at this frequency (Table 1). In porcine subjects there is unavoidable collateral injury due to the narrow width of the third ventricle, but in humans, where the ventricle is 5–6 mm in width, the focal region could fit entirely within the ventricle, likely without injury to the walls.

Treatment parameters, estimated in situ peak rarefaction pressures, and results of third ventriculostomies in 9 swine treated using the ExAblate 4000 MRlgFUS system

Table 1

Frequency (kHz)	Acoustic Power (W)	Simulated (MPa)	dT/dt (MPa)*	McDannold (MPa) [†]	Pulse Duration (sec)	No. of Pulses	Successful?	Size (mm)	Vessel Damage (mm)	Rim of Damage (mm)
650	1000	27.5	15.7	15.0	0.1	1	yes	2.3	0.9	0.9
650	2200	29.8	17.0	16.2	0.1	2	no			
650	1500	36.1	20.6	19.6	0.3	3	no			
650	1000	39.7	22.7	21.6	1	1	yes	6.6	0.6	0.6
650	2000	44.7	25.5	24.4	1	1	yes	9.2	1.5	0.7
650	2000	47.0	26.8	25.6	1	1	yes	9.3	0.4	0.4
650	1500	50.4	28.8	27.4	1	1	yes	8.5	1	0.6
650	1900	20.6	11.8	11.2	5	1	no			
230	2900	16.3	9.3	8.8	1	1	yes	4.7	3.2	0.7

*The error was estimated to be ± 9% without skull and ± 22% with skull. This method extended to 230 kHz assumed a gain proportional to frequency. The error was attributable to the uncertainty in the physical parameters used in the model, as well as the measurement error in skull transmission.

[†]The calibration error was reported to be ± 10%,²¹ leading to an estimate of ± 24% for our measurements. The increased error is due to the combination of uncertainty in the transmission through skull, the attenuation of brain tissue, and the intensity loss due to steering. This method extended to 650 kHz similarly assumed an increased gain proportional to the frequency.

Table 2
Physical properties used in the estimation of in situ peak rarefaction pressures

Parameter	Description	Value
ρ_b	density	1030 kg/m ³
c_b	speed of sound	1540 m/s
α	attenuation *	5 Np/m/MHz
α_a @ 700 kHz	absorption *	1.4 Np/m
$C_m^{\dagger}$	specific heat	3.85 kJ/kg/°C

* From Goss et al.¹¹

[†] From Werner and Buse.³⁶