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In vivo transcranial brain surgery with an ultrasonic time reversal mirror

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Object. High-intensity focused ultrasonography is known to induce controlled and selective noninvasive destruction of tissues by focusing ultrasonic beams within organs, like a magnifying glass concentrating enough sunlight to burn a hole in paper. Such a technique should be highly interesting for the treatment of deep-seated lesions in the brain. Nevertheless, ultrasonic tissue ablation in the brain has long been hampered by the defocusing effect of the skull bone.

Methods. In this in vivo study, the authors used a high-power time-reversal mirror specially designed for noninvasive ultrasonic brain treatment to induce thermal lesions through the skulls of 10 sheep. The sheep were divided into three groups and, depending on group, were killed 1, 2, or 3 weeks after treatment. The thermal lesions were confirmed based on findings of posttreatment magnetic resonance imaging and histological examinations.

After treatment, the basic neurological functions of the animals were unchanged: the animals recovered from anesthesia without any abnormal delay and did not exhibit signs of paralysis or coma. No major behavioral change was observed.

Conclusions. The results provide striking evidence that noninvasive ultrasonographic brain surgery is feasible. Thus the authors offer a novel noninvasive method of performing local brain ablation in animals for behavioral studies. This technique may lead the way to noninvasive and nonionizing treatment of brain tumors and neurological disorders by selectively targeting intracranial lesions. Nevertheless, sheep do not represent a good functional model and extensive work will need to be conducted preferably on monkeys to investigate the effects of this treatment.

Key Words • ultrasonography • noninvasive surgery • high-intensity ultrasonography • sheep

Radiotherapy is currently proposed as an alternative to surgery in cases of benign brain tumors, brain metastases, or vascular malformations previously considered inoperable because they were located too deep inside the brain or too close to vital structures. Whole-brain radiotherapy or more precise stereotactic radiotherapy can be performed separately or combined.[19] The precision of GKS has long been demonstrated and its benefits are great for brain tumors. Nevertheless, the question of whether GKS can induce secondary neoplasia has been raised.[11] Therefore, the development of new alternatives is of interest. Such alternatives could be combined with GKS or performed separately. Tissue ablation with focused ultrasonographic beams has shown significant potential in the treatment of tumors in various organs[3,14,17,24,29] and should be theoretically suited to noninvasive and nonionizing brain surgery. Thus, ultrasonic beams have been used to induce a high temperature rise in the brains of animals[9,20,30] and a low temperature rise in those of humans (combined with radiotherapy).[15] In all studies, however, a pretreatment craniotomy was necessary because the skull bone deflects the therapeutic beam.[8,10,13,31] Recently McDannold et al.[20] demonstrated MR imaging and guidance of high-intensity focused ultrasonic beams in the brains of monkeys, but they performed a craniotomy to allow the beam to pass into the brain. Because a craniotomy was performed, the ultrasonic treatment is no longer considered noninvasive, and therefore its clinical interest is limited.

In the 1990s, transcranial adaptive focusing techniques were proposed to compensate the distortions induced by the skull bone. Basically, a distorted wavefront is emitted by an array of transducers in such a manner that it generates a converging spherical wavefront after propagation through the skull. The key point is to predict how the skull will affect the beam to compute the set of emission signals. Two approaches have been introduced based on the presence of an acoustic source at the desired focus location. The wavefront originating from this point is recorded on the therapeutic array. The first approach consists of detecting the phase of signals received at one frequency on each

Abbreviations used in this paper: GKS = Gamma Knife surgery; MR = magnetic resonance.

transducer and in reemitting the opposite phase at the same frequency (known as phase compensation[16]). The second approach consists of time reversing the recorded signals, that is, signals that arrive first are emitted last. Metaphorically speaking, this idea corresponds to allowing the slowest competitors to start in advance, so that that all competitors arrive together at the finish line. Physically, time reversal compensates the phase at each frequency.[25] To use these focusing techniques transcranially in practice, large-scale, high-power phased arrays have been specially developed during the last decade.[2,6,21] One group recently developed an MR imaging–compatible 500-element array capable of producing up to 1080 acoustic watts. The group tested the device on rabbits whose skulls had been trephined, and the animals were then placed behind a formalin-fixed human skull.[15] Thermal lesions were achieved in the rabbit brain because of prior calibration with a hydrophone located at the geometric center of the array in the absence of the rabbit to correct for the skull distortion. Only the phase of the ultrasonic wave was corrected; no amplitude variation was considered. This study was an important step toward transcranial ultrasonic therapy but, as stated in the group's conclusion, before clinical trials are performed the system needs to be tested in a large-animal model. We conducted the present study to precisely induce thermal lesions transcranially in vivo in large animals. To induce thermal lesions through the skull of living animals, one needs more power than that used in the previously mentioned rabbit model.[16] Indeed the coupling with the skull is more complex than in an ex vivo skull without skin fixed in a water tank. Moreover, for the treatment of large tumors beam steering is required given that the targeted location will not necessarily correspond to the geometric center of the therapeutic array.

The therapeutic array developed by our group[21] and used in this study is made of 277 transducers able to emit up to 2400 acoustic watts. Given fully programmable electronics, the correction technique used in this study is time reversal, and both phase and amplitude distortions are taken into account.

Materials and Methods

High-Power Prototype

To induce in vivo local ablation in the brain through an intact skull, a high-power prototype has been specially designed and built. The device comprises 277 individual transducers specially designed by Imasonic (Besançon) and mounted on a spherical surface with a semi-random distribution (Fig. 1 *left*). A specific piezocomposite technology called Imasonic HI2 has been developed to reach acoustic levels that could not be obtained using former piezoelectric technology.[2] The central frequency was set to 1 MHz because skull bone absorption rapidly increases with frequency. To correct the aberrations induced by the skull bone, the active element size has to be smaller than the correlation length of the skull (10 mm at 1 MHz); we set it to 8 mm. In front of the array, a water bath was mounted to provide a flexible coupling window that fit the outer surface of the skull (Fig. 1 *right*). The water bath was coupled to a cooling system to limit any temperature rise in the skin and bone during treatment. Each transducer was driven by its own fully programmable 18-W electronics channel. The electronics can be seen in Fig. 1 *left*, behind the therapeutic array.

Animal Model

Although this prototype has been designed for noninvasive transcranial brain treatment in humans, we first tested it in vivo in 10 sheep. This large-animal model was chosen because the size of these animals' brains is sufficient for the study and the ultrasonic properties of its skull bone are close to those of the human skull. At this stage, no tumor was implanted in the animal's brain because our aim in the present study was to check whether it is possible to concentrate enough energy through the skull to induce thermal lesions in deep-seated tissues (in this instance 3–4 cm deep).

Animal Preparation

The animal preparation and treatment planning were approved by the ethical committee of the IMM Research Group. Experiments were conducted in a sterile environment. Each sheep was tranquilized using Hypnovel (intravenous midazolam, 0.5 mg/kg), and then it was deeply anesthetized with Pentothal (intravenous thiopental, 10 mg/kg). The animal's rectal temperature was monitored using a copper-constantan thermocouple. The hair on the animal's head was removed with hair clippers and depilatory cream.

Ultrasonic Beam Treatment

A skin incision was made laterally, immediately behind the external orbital pillar, and a 10-mm-diameter bur hole was drilled to insert a 4-mm trocar (Fig. 2 *left*). The animal was then positioned in front of the array (Fig. 2 *right*). A 3-mm needle hydrophone (Onda Corp.) was inserted inside the trocar at the target location. In all animals, the target region was located deep in the brain, close to the thalamus. We chose to exclude the frontal lobes (to avoid the reflection of ultrasonic beams onto the frontal sinuses), the ventricles (to be sure the site was in the brain parenchyma), and the brainstem (to avoid life-threatening lesions). A 10-cycle 1-MHz signal was emitted by the hydrophone. After propagation through the skull bone, the distorted wavefront was recorded on the therapeutic array (Fig. 3 *left*). The wave

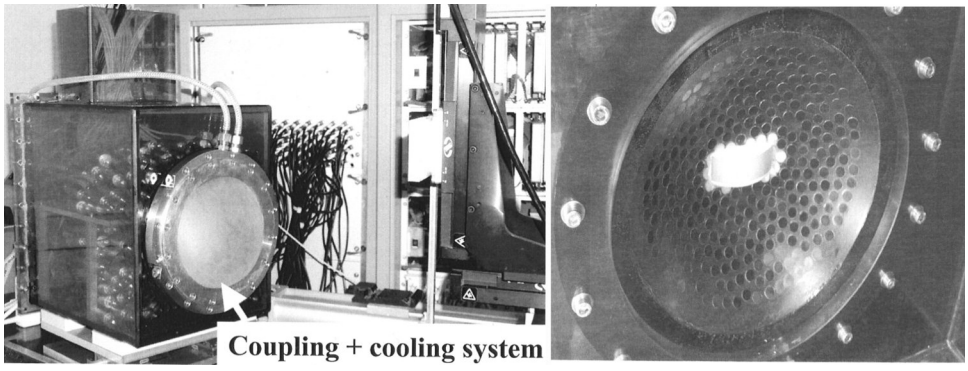

FIG. 1. Photographs showing a high-power time reversal prototype. *Left:* Large view of the high-power prototype with its cooling system. *Right:* Close-up view of the 277 therapeutic transducers mounted on a spherical surface. An echographic array has been inserted in the center of the array to guide the global positioning.

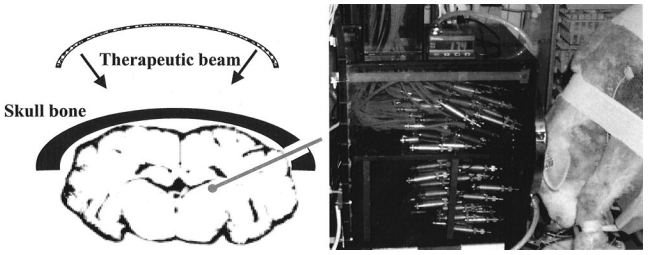

FIG. 2. Treatment setup. *Left:* Illustration of the treatment. The hydrophone is inserted at the target location laterally through a bur hole and ultrasonic treatment is performed transcranially from the top of the head. *Right:* Photograph showing the clinical setup: the animal's head is located in front of the therapeutic array.

front was then time reversed to compensate for diffraction and refraction effects induced by the skull bone.[15] Concretely, each transducer was driven by its own electronics, including a programmable generator capable of synthesizing the temporally inverted signal stored in memory. Once the hydrophone was removed, the time-reversed signals were again emitted to focus back through the skull toward the initial position (Fig. 3 *right*). Because of the time invariance of the wave equation, the ultrasonic wave propagates back to the initial location as if a movie depicting its propagation toward the array were played backward. The efficiency of time-reversal focusing can be seen in Fig. 4, in that energy repartition in the focal plane is plotted on a linear scale. Without any correction there is a defocusing effect of the skull (Fig. 4 *left*), whereas the time-reversal technique provides a good focusing quality (Fig. 4 *right*).

Imaging Modalities

Posttreatment images were obtained using a 1.5-tesla clinical MR imaging unit (Genesis-Sigma, General Electric Medical Systems). Fast spin echo T_2-weighted images were acquired (TR 5440 msec, TE 107 msec, echo train length 16, matrix 192 × 192, field of view 12 cm, slice thickness 2 mm, 2.2 mm between images, and three averages). Imaging planes were chosen to cover the entire brain.

Histological Analysis

The animals where killed by an overdose of pentobarbital. The entire brain was removed and fixed in 4% formaldehyde for 1 month. Five-millimeter-thick slices were cut along frontal planes and 0.5 × 0.5–cm samples were selected for histological examination. Routine staining (H & E and Masson trichrome) was used to examine and select the relevant slices.

Results

Because of the time-reversal correction, the energy deposition at the focus was measured in vivo and was found to be on average 20 times higher than that without any correction. The initial planned treatment was the following: a 10-second sonication session at the maximum power repeated 10 times in the same location with a 10-second delay between the sessions to allow the animal's skin temperature to return to the baseline value. The water-cooling system was used during the entire treatment, and its temperature was set to 10°C. It appeared that cooling between sessions was not sufficient, and some skin was burned on the first two sheep. Burns could be seen on the outer surface of the skull after these animals were killed. For this reason, we extended the delay between sessions to 15 seconds and we inserted a thermocoupling device between the water balloon and the skin to measure the temperature in real time. During treatment, the mean temperature of the skin surface was 40°C and between experiments it returned to a mean baseline temperature of 20°C. With such delays, no skin burns were noted on the other animals.

All tissue damage observed during the histological examination corresponded to the end position of the needle hydrophone. None of the samples obtained from other regions displayed damage.

The animals were awakened after treatment and divided into three groups depending on the times of their scheduled deaths and examinations: 1 (two animals), 2 (four animals), and 3 (four animals) weeks later. From a behavioral point of view, the animals did not appear to be different before and after treatment. This indicates that during the experiments no functional area was affected by the needle and that the ultrasonic treatment did not significantly alter the brain during propagation of the wave from the outer surface of the skull to the targeted focal spot. After the animals had been killed, their brains were removed and fixed in formaldehyde for macroscopic and histological examinations. Magnetic resonance imaging was performed before the pathological examination.

For animals killed less than 8 days after treatment, necrotic tissue was visible on T_2-weighted MR images (Fig. 5 *left*).

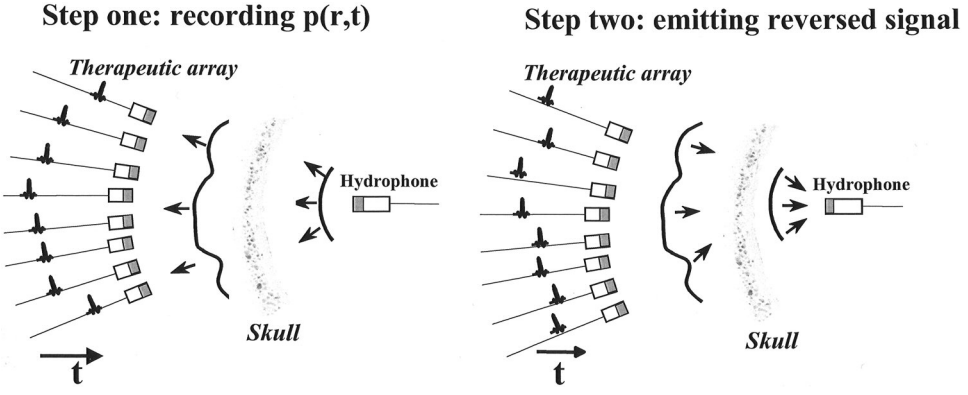

FIG. 3. Schematic of the time reversal correction. *Left:* First step. The wavefront emitted by the hydrophone is recorded on the therapeutic array after propagation through the skull. The equation p(r, t) represents pressure (p) as a function of space (r) and time (t). *Right:* Second step. The time-reversed signals are reemitted and focused back to the initial location.

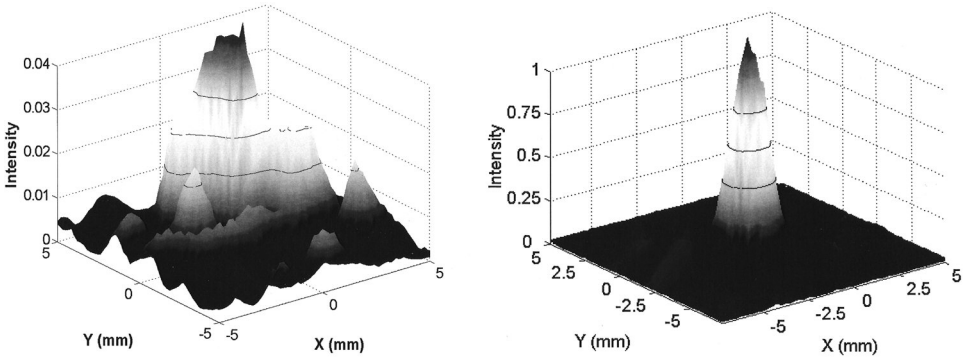

FIG. 4. Graphs showing the defocusing effect of the skull. The energy repartition in the focal plane is plotted in a linear scale without any correction *(left)* and with time-reversal correction *(right)*.

The presence of thermal lesions was confirmed in seven sheep during histological examinations (Fig. 5 *right*). These lesions comprised large areas of acidophilic necrosis surrounded by mononucleated cells. It is important to note that because of the focusing quality and the adjusted sonication time, no lesions were found in tissues surrounding the targeted location or in selected parts of the brain close to the inner surface of the skull. No lesions were found in three animals because the needle path could not be seen clearly on gross histological examination. In these animals no clear guidance was available, and we could not locate the treated area using the gross histological examination that we planned for the study. We were not able to select a tissue sample in these three animals for pathological examination.

The cigar-shape of the half-width focal spot at the geometrical focus was 4.2 mm long and 0.8 mm in diameter. Due to thermal conduction during heating, the expected size of the lesion was 6 × 2 mm. The mean size of the lesions on histological examination was 6.75 ± 2.4 mm × 3.6 ± 1.4 mm.

Discussion

Correction of the Defocusing Effect of the Skull Bone

Even though high-intensity focused ultrasonic therapy is particularly suited to target deep areas of the brain noninvasively, its use has long been limited by the defocusing effect of the skull bone.[8,10,31] In the 1990s, the idea of correcting the defocusing effect of the skull with adaptive techniques was developed.[15,23,25]

In this study, we designed a high-power prototype and successfully tested it in 10 sheep. This prototype is made of 277 individual transducers that are able to correct the phase shifts induced by the skull. Concretely, this correction is done by time reversing the signals recorded after propagation through the skull bone:[7] the fastest signals arrive through the skull bone first, and they are bounced off last. Thanks to this correction, the signals emitted by all the ultrasonic transducers arrive at the focal point at the same time despite the distortions induced by the skull. The energy deposition at the focus was measured in vivo to be on av-

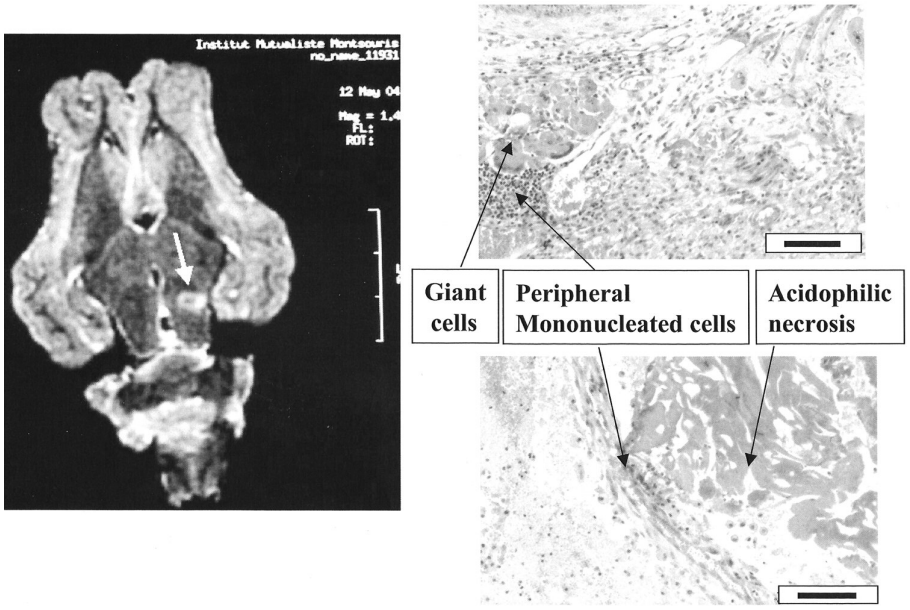

FIG. 5. Thermal lesions. *Left:* A T_2-weighted MR image. The *arrow* points to a hypointense signal surrounded by a hyperintense signal at the treatment location. *Right:* Photomicrograph confirming lesions. A large area of acidophilic necrosis surrounded by mononucleated cells can be seen. H & E, bar = 100 μm.

erage 20 times higher than that without any correction. The estimated energy deposition at the focus was 1500 W/cm^2. This was enough to induce a thermal lesion in the brain, as confirmed by the histological analysis. It confirms the feasibility of performing local ablation of tissues through the skull bone with high-intensity focused ultrasonography.

Protection of Skin and Bone

In recent years, authors of clinical trials have evaluated the clinical efficacy of a number of high-intensity ultrasonic devices worldwide[17,32] that have mainly been used to treat prostate[12,26] and liver tumors.[18] It has been reported that focusing high-intensity ultrasonic beams deep inside the tissues can sometimes cause skin burns.[17,24,28] Indeed, even though the pressure field on the skin is considerably lower than at the tumor focus, if the treatment time is too long the thermal dose to the skin can be higher than the necrosis threshold. To avoid skin burns, we included a cooling system in which circulating water is maintained at 10°C.

After two trials with the first two animals, an appropriate treatment was determined: 10 seconds of ultrasonic beam delivery at the maximum power repeated 10 times in the same location with a 15-second delay between the sessions to allow the skin temperature to return to the baseline value (that is, a mean 20°C measured in real time with a thermocouple; the water-cooling system is used during the entire treatment session). With such parameters, no skin burn was noted on the other animals. After the skull bone had been removed so that we could stain brain tissue for histopathological analysis, we found on gross examination that no burns were sustained by the outer or inner surface of the skull bone. This is an important in vivo result as some questions have been raised recently about the difficulty encountered in avoiding skin burns when performing high-intensity focused ultrasonic treatment of the brain.[5] Connor and Hynynen[5] have shown numerically that it should be possible to avoid overheating the skull when targeting the cranial base but might be more difficult to avoid such a problem when targeting more rostral locations (< 4 cm from the outer surface of the skull). In our study we have demonstrated that it is possible to induce thermal lesions transcranially without inducing skin burns: it can be done at least for targets located 4.5 to 2.5 cm away from the skull surface for large animals like sheep. One has to notice that an active cooling system was used during the entire treatment time; the volume of degassed water contained in the coupling system (Fig. 1 *left*) was continuously exchanged and chilled down to 10°C.

Neurological Outcome

A basic neurological score established by the IMM research laboratory as been applied to our study, and it is summarized in Table 1. The 10 animals treated with the planned protocol presented here obtained the top assessment, that is, "normal" for each item. Nevertheless, sheep do not represent a good functional model and a primate model would be a more compelling test of possible behavioral changes induced by high-intensity focused ultrasonic beams. This will be done in a further work.

TABLE 1

Basic neurological scoring devised by the IMM Research Group

	Parameter		
Neurological Score	Consciousness	Appetite	Motor Function
0	coma	does not drink	does not stand
1	stupor	does not eat	does not walk
2	exhaustion	eats less	walks w/ difficulty
3	normal	normal	normal

Conclusions

For the first time, transcranial thermal lesions have been induced in vivo through intact skulls of large animals by using high-intensity focused ultrasonic beams. This is a major breakthrough toward noninvasive and nonionizing brain treatments. Such a technique would be particularly suited to target deep-seated areas of the brain to treat tumors or neurological disorders such as Parkinson disease or epilepsy. It also offers a new way to perform noninvasive neuroablation in behavioral studies in animals.[17,22,27] At this stage, the feasibility of the treatment was validated using a hydrophone implanted inside the tissues. It has already been shown that the presence of a hydrophone could be simulated by setting a virtual acoustic source in a 3D finite differences simulation code based on computed tomography images of the skull.[1,4] In that case, the defocusing effect of the skull bone is not recorded experimentally on the therapeutic array but simulated. This completely noninvasive procedure will be validated with the same prototype in further work in which monkeys are used. Before safe and effective clinical treatments can be developed, extensive work will also have to be conducted to investigate the change in neurological function associated with a given energy deposition.

Acknowledgment

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Dedication

In memory of Philippe Boch who initiated the authors' collaboration.

Disclosure

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