

High-Intensity Focused Ultrasound for Noninvasive Functional Neurosurgery

Ernst Martin, MD,¹ Daniel Jeanmonod, MD,² Anne Morel, PhD,² Eyal Zadicario, MSc,³ and Beat Werner, MSc¹

Transcranial magnetic resonance (MR)-guided high-intensity focused ultrasound (tcMRgHIFU) implies a novel, noninvasive treatment strategy for various brain diseases. Nine patients with chronic neuropathic pain were treated with selective medial thalamotomies. Precisely located thermal ablations of 4mm in diameter were produced at peak temperatures of 51°C to 60°C under continuous visual MR guidance and MR thermometry. The resulting lesions are clearly visible on follow-up MR imaging. All treatments were well tolerated, without side effects or neurological deficits. This is the first report on successful clinical application of tcMRgHIFU in functional brain disorders, portraying it as safe and reliable for noninvasive neurosurgical interventions.

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For over 50 years researchers have been seeking a way to perform noninvasive thermal ablation for brain treatments.^{1,2} Recent technical advances have made magnetic resonance (MR)-guided high-intensity focused ultrasound (MRgHIFU) a firmly established modality for noninvasive surgery under closed-loop image guidance and control throughout all steps of the intervention process.^{3–5} MR imaging (MRI) allows for precise intraprocedural localization of the ablation target,⁶ definition and verification of safety margins for the ultrasound treatment, real-time monitoring of thermal ablation dynamics,⁷ and intratreatment and posttreatment assessment of intervention results. Thanks to its noninvasiveness, MRgHIFU minimizes the risk of bleeding and infection and avoids collateral damage to nontargeted tissue.⁸ In addition, it does not involve ionizing radiation. Transcranial application of MRgHIFU, therefore, promises to become an impor-

tant new modality for neurosurgical interventions^{9,10} and is envisioned to enable novel treatment strategies against a variety of brain diseases.^{5,11–13}

Based on our long-term clinical experience in functional neurosurgery of neuropathic pain with stereotactic interventions in the medial thalamus,^{14–16} we developed intervention processes to access ablation targets in the brain noninvasively, using transcranial MRgHIFU (tcMRgHIFU). Following preclinical studies with phantoms, biological tissues and human *ex vivo* head preparations, a clinical phase I study was initiated to investigate the feasibility, reproducibility, accuracy and safety of tcMRgHIFU for functional neurosurgery. The study was approved by the ethics committee of the University and the State of Zurich.

Patients and Methods

Patients

Having obtained fully informed written consent, nine patients scheduled for a selective central lateral thalamotomy (CLT)¹⁶ against chronic therapy-resistant neuropathic pain were enrolled. Therapy resistance was established by lack of efficiency of antiepileptic and antidepressant drugs. The first nine interventions encompassed patients aged 45 to 75 years suffering from pain in the face (three patients), neck (one patient), lower extremity (two patients), upper extremity (two patients) and hemibody (one patient), of central (three patients) or peripheral (six patients) origin. The nine causal lesions at the origin of the different neuropathic pain syndromes were amputation, nerve compression by disc prolapse or neurinoma, zoster infection, nerve trauma, brachial plexus avulsion, and thalamic infarct. One additional patient suffered from idiopathic trigeminal neuralgia, and another from a neuropathic pain syndrome in the context of cervical dystonia. The duration of pain in these patients was between 1.5 and 17 years (mean, 7.5 years).

Surgery and Intraoperative Observations

The noninvasive neurosurgical interventions were performed in a clinical 3T MR-system (Signa HDx; GE, Milwaukee, WI) using a clinical system for tcMRgHIFU surgery (ExAblate 4000; InSightec, Tirat Carmel, Israel) featuring a hemispheric 1,024-element phased array transducer operating at 650kHz.

The fully shaved patient's head was immobilized within a MR-compatible frame (Radionics, Burlington, MA) and carefully positioned in the helmet-like cavity of the ultrasound transducer (Fig 1). The space between the transducer and head surface was sealed with a flexible membrane and filled with degassed water for ultrasound coupling. The water circulated at 16°C for continuous scalp cooling. The ablation target, ie, the posterior part of the thalamic central lateral nucleus, was localized on 3D T1-weighted MRI (T1WI) using the multiarchitectonic Morel atlas of the human thalamus and basal ganglia.¹⁷ The coordinates of the sonication lesions were determined and entered into the planning software of the tcMRgHIFU system. Intrinsically, tcMRgHIFU sonications are not limited by trajectory restrictions and offer several degrees of freedom to tailor the sonication pattern for

From the ¹MR-Center, University Children's Hospital Zurich, and ²Department of Functional Neurosurgery, University Hospital Zurich, Zurich, Switzerland; and ³InSightec, Ltd., Tirat Carmel, Israel.

All authors contributed equally to this work.

Address correspondence to Dr Ernst Martin, MR-Center, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland. E-mail: ernst.martin@kispi.uzh.ch

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Fig 1. Patient prepared for transcranial magnetic resonance (MR)-guided high-intensity focused ultrasound (tcMRgHIFU) intervention. The head is immobilized within a stereotactic frame. The transducer is positioned using a three-axis mechanical positioner. The flexible membrane seals the space between patient head and transducer, which is filled with degassed water. The bore of the 3T MR scanner is visible in the background.

optimal target volume coverage: peak temperature, sonication duration, and combination of multiple sonication lesions.

Before the actual treatment phase of the tcMRgHIFU intervention it was confirmed that the thermal hot spot was centered in the target location. For this, several low-power sonications of 10 seconds to 20 seconds duration were applied to induce peak temperatures of 39°C to 42°C. These temperatures are known to be below the ablation threshold but are easily visualized on MR thermometry images to assess exact position and size of the hot spot and the overall safety profile of the applied sonication parameters¹⁸ (Fig 2A).

During treatment several high-power sonications were applied in an iterative process guided by MRI and MR thermometry. In order to induce local tissue ablation the acoustic power was stepwise increased from sonication to sonication to finally achieve a peak temperature at the target between 51°C and 60°C (Fig 2B). Typically, continuous wave sonications of 10 seconds to 20 seconds duration, up to a maximum acoustic power of 1,200W and 800W, respectively, corresponding to 12,000J per sonication, were applied.

Patients were fully awake and responsive during all stages of the intervention. The only medication administered before the procedure comprised an oral benzodiazepine. In two cases a subcutaneous opiate injection was necessary because of back pain due to lying motionless supine on the MR table for an extended period of time. During the entire series of sonications, patients were monitored and questioned repeatedly to ensure their neurological integrity and to assess changes in pain quality, extension, and intensity, or other sensations experienced during the treatment.

Results

Selective CLT against chronic neuropathic pain were applied in nine patients using the novel, noninvasive

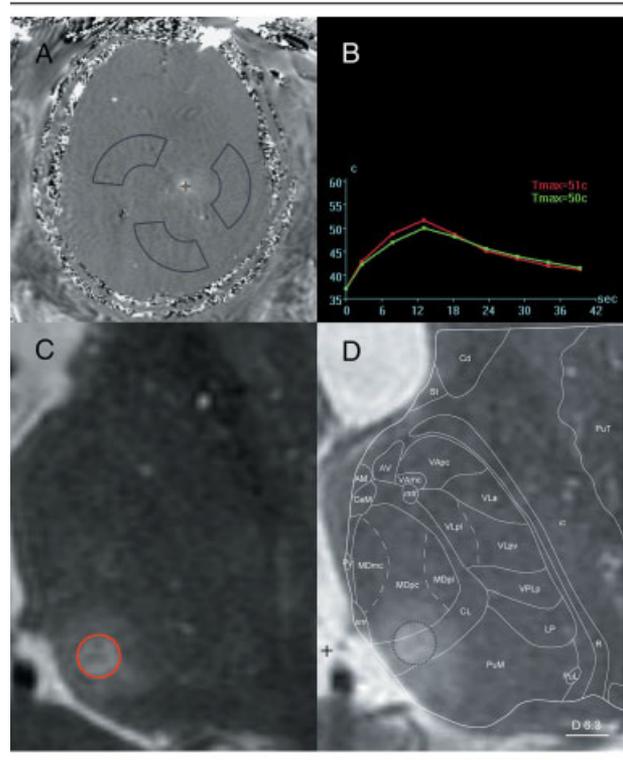


Fig 2. Magnetic resonance (MR) image guidance of transcranial MR-guided high-intensity focused ultrasound (tcMRgHIFU) intervention. (A) Thermal map on axial plane at the level of the third ventricle. Thermal maps are refreshed at intervals of 3 to 5 seconds to monitor localization and dynamics of temperature rise during sonication and subsequent temperature relaxation during cooling period. The planned sonication target in the posterior part of the central lateral thalamic nucleus (blue circle); the pixel with the highest temperature at the end of sonication (red cross). The three wedge-shaped forms are placed by the operator to balance background noise in thermal calculations. (B) Temperature evolution during a therapeutic sonication of 12 seconds duration using 850W in the voxel of highest temperature (red), with time resolution = 4 seconds and monitored cooling period after sonication = 30 seconds; temperature evolution of average temperature of the neighboring voxels around the temperature maximum (green). (C) (red circle) Contour line of thermal dose corresponding to 17 cumulative equivalent minutes (CEM) 43°C (see Results) at the target location superimposed on the T2-weighted imaging (T2WI) obtained 48 hours after treatment. (D) Stereotactic reconstruction of tcMRgHIFU-guided central lateral thalamotomy (CLT). The outline of the lesion (dotted circle) corresponds to the extent of zone II (3–5mm diameter) seen on axial T2WI taken 48 hours postoperatively. The location of the CLT is determined by projecting the corresponding atlas map (6.3mm dorsal to intercommissural plane) onto the T2WI image using the position of the posterior commissure (black cross) for anteroposterior alignment. Scale bars = 4mm. For abbreviations see Ref. 17.

tcMRgHIFU technology. Patients were monitored continuously before, during, and after each sonication period, were asked for their subjective experience (pain reduction, somatosensory improvements, vestibular feelings, paresthesias, and dysesthesias), and were examined to exclude any motor or somatosensory deficit. All treatments were well tolerated and no side effects or neurological deficits were observed. Operating at peak temperatures of 51°C to 60°C (except in the very first patient, where the peak temperatures were kept below 50°C for safety reasons) under closed-loop MR guidance, precisely located lesions of 3mm to 5mm diameter were evident in 48-hour postoperative MRI. Pain relief 2 days after the interventions ranged from 30% to 100% (mean, 68%). Patients reported sonication effects during the procedure, such as pain relief (nine patients), somatosensory improvements (five patients), vestibular feelings (five patients), paresthesias (three patients), or dysesthesias (seven patients) in and around the pain area. These symptoms had already been observed in some patients at focal temperatures below 50°C.

MRI of the sonication lesions immediately following the intervention (in two patients) and 48 hours after the intervention (in all nine patients) revealed three concentric zones on T2-weighted MRI (T2WI). They consist of a somewhat heterogeneous isointense to hypointense center (zone I) surrounded by a strongly hyperintense region (zone II). Zone II is sharply demarcated by a small hypointense rim toward an outer slightly fuzzy and irregularly-shaped area (zone III) of lower hyperintensity (Fig 3A, B). This corresponds well to earlier studies on animal brains.^{6,8} The irregularly bordered outer zone III extends up to a maximum diameter of 10 to 12mm at 48 hours postintervention and represents the perifocal edema. It is best seen as a diffusely hyperintense area on T2WI (Fig 3A, B).

Depending on the peak temperature achieved, the size of zone I immediately following the intervention and 48 hours postoperatively is 1 to 2mm in diameter on axial planes and 2 to 3mm in length on sagittal and coronal slices. The hyperintense zone II has a diameter of 3 to 4mm and a length of 4 to 5mm. These inner two zones, zones I and II, most probably correspond to the areas of coagulated and necrotic tissue⁸ and are immediately and 48-hours postoperatively strongly hyperintense on isotropic diffusion images (Fig 3E, F), indicative of coagulation necrosis and cytotoxic edema. They are slightly hypointense on apparent diffusion coefficient maps and on T1WI, with a strong ring enhancement of about 1 to 2mm thickness after administration of an intravenous contrast agent immediately after the intervention (Fig 3C), but almost unapparent at 48 hours follow-up (Fig 3D).

Previous reports based on in vivo data in rabbit brain show that a thermal dose equivalent of 17 min-

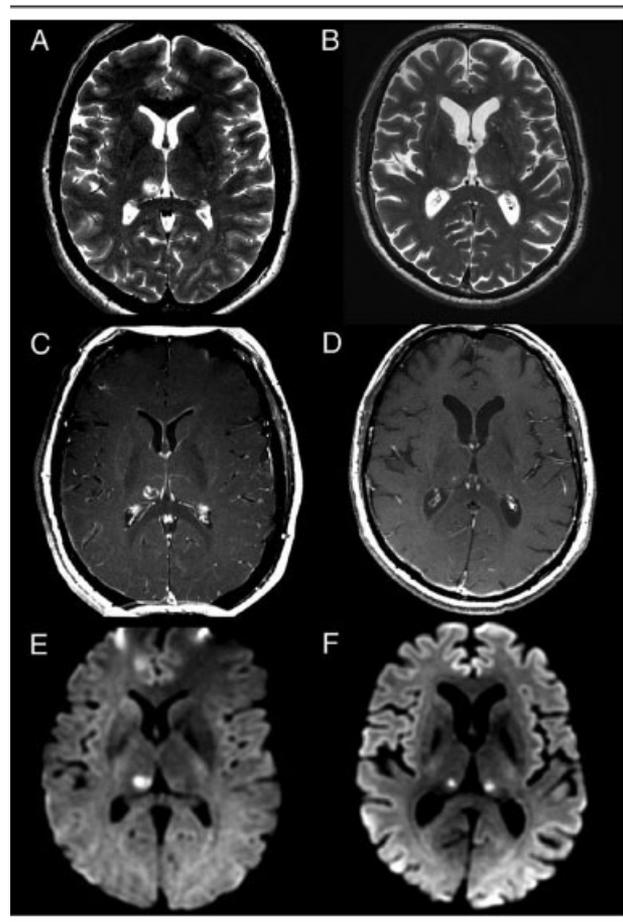


Fig 3. Posttreatment magnetic resonance (MR) images. (A, C, E) Axial T2-weighted image (T2WI), postcontrast T1-weighted image (T1WI), and isotropic diffusion tensor image, respectively, of patient 2, obtained immediately after treatment with tcMRgHIFU. Two sonication lesions of 3–5mm diameter were placed into the right posterior part of the central lateral nucleus of the thalamus (for image description see Results). (B, D, F) Axial T2WI, postcontrast T1WI, and isotropic diffusion tensor image, respectively, of patient 3, obtained 48 hours after treatment with tcMRgHIFU. One sonication lesion was placed bilaterally in the posterior parts of each central lateral thalamic nucleus (for image description see Results).

utes at 43°C (ie, 17 cumulative equivalent minutes [CEM] 43°C) will result in 50% tissue damage.¹⁹ In accordance with these findings, the combined size of zones I and II as seen on T2WI (Fig 3A, B) after treatment exactly matches the area that accumulated more than 17 CEM 43°C on MR thermometry images during treatment (Fig 2C).

The precision of tcMRgHIFU targeting was calculated by comparing the centers of zone II on T2WI 48 hours postoperatively to presurgical stereotactic coordinates of the ablation targets. So far, for nine targets in five patients the median/mean \pm standard deviation (SD) are as follows: (1) dorsoventral 0.5/0.61 \pm

0.56mm; (2) anteroposterior $1.5/1.16 \pm 0.57$ mm; and (3) mediolateral $0.5/0.96 \pm 0.87$ mm.

Discussion

The preliminary findings of our ongoing clinical phase I study on nine patients indicate for the first time that tcMRgHIFU is a safe, reliable, and precise modality for noninvasive neurosurgical interventions, and highlight the potential of this novel technology. All treatments could be safely performed and successfully executed to the planned endpoints due to high-field MRI guidance, closed loop feedback and intraoperative control concepts implemented in the tcMRgHIFU system. The sonication protocol allows for optimal target coverage: (1) by applying multiple sonication lesions, and (2) by freely choosing the position of the sonication lesions without trajectory restrictions. Being noninvasive, all treatments were performed on fully awake patients as an outpatient procedure. Although pain relief was immediate in all treated patients, prior studies of thalamotomy have suggested that such relief might be transient. Our previous results with radiofrequency CLT on a large series of patients¹⁶ demonstrate long-term (mean follow-up 3 years 9 months) pain relief between 50% and 100% in 53% of patients. Follow-up MRI studies (as implemented here), physiological tests (quantitative electroencephalography [EEG] with spectral analysis and source localization), as well as clinical examinations (pain questionnaire, visual analog scale, and neurological examination by independent observer) are planned at 3 and 12 months postoperatively to document in detail the long-term postsonication evolution of the patients.

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