Received: November 30, 2012 Revised: March 22, 2013 Accepted: April 2, 2013

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12075

Low-Intensity Focused Ultrasound Pulsation Device Used During Magnetic Resonance Imaging: Evaluation of Magnetic Resonance Imaging-Related Heating at 3 Tesla/128 MHz

Alexander S. Korb PhD*; Frank G. Shellock, PhD†; Mark S. Cohen, PhD*‡; Alexander Bystritsky, MD, PhD*

Objective: The objective of this study was to determine magnetic resonance imaging (MRI)-related heating for a low-intensity focused ultrasound pulsation (LIFUP) device used during MRI performed at 3 T/128 MHz.

Materials and Methods: A special phantom was constructed to mimic the thermal properties of the human brain, and a piece of human temporal bone (skull) was embedded on top. Four fluoroptic thermometry probes, placed above and below the skull, were used to measure temperature changes during MRI (3 T/128 MHz; scanner-reported head average specific absorption rate 1.1–2 W/kg) with and without concurrent LIFUP sonication. LIFUP sonication was applied using a focused ultrasound device (BXPulsar 1001, Brainsonix, Inc., Los Angeles, CA, USA) at a derated spatial-peak temporal-average intensity of 3870 mW/cm^2.

Results: MRI performed at relatively high specific absorption rate (SAR) caused a slight elevation in temperature ($\leq$0.6°C). Concurrent use of MRI at a medium-strength SAR and LIFUP sonication resulted in maximum temperature rise of 3.1°C after 8 min of continuous use.

Conclusions: Under the specific conditions utilized for this investigation, LIFUP sonication does not appear to present significant heating risks when used concurrently with MRI. This information has important implications for the use of the LIFUP sonication in human subjects undergoing MRI at 3 T/128 MHz.

Keywords: Device safety, MRI, neuromodulation, therapeutic ultrasound.

Conflict of Interest: Dr. Bystritsky is the founder of Brainsonix, Inc. Drs. Korb, Shellock, and Cohen report no conflicts of interest.

INTRODUCTION

Low-intensity focused ultrasound pulsation (LIFUP) is a promising new technique for noninvasive neuromodulation (1). LIFUP utilizes low-energy ultrasound (US) waves that pass through the skin and skull without surgery and which can be focused almost anywhere in the brain to modulate neural activity (2). LIFUP neuromodulation has the potential to treat a wide range of neurologic and psychiatric conditions, including epilepsy, obsessive–compulsive disorder, and depression (3–5).

Currently, therapeutic devices for neuromodulation in the brain suffer from several limitations, including invasiveness and lack of spatial specificity. For example, deep brain stimulation (DBS) has the advantages of being highly focused and of being able to target structures deep in the brain, but it requires invasive surgery (e.g., (6–8)). Vagus nerve stimulation, while not involving penetration through the skull, still requires surgery and does not have high spatial specificity (9). By contrast, repetitive transcranial magnetic stimulation has the benefit of being noninvasive but has severely limited spatial resolution, particularly at depths below superficial cortex (10). Similarly, cranial electrotherapy stimulation and transcranial direct current stimulation, while also noninvasive, lack spatial specificity (11).

In contrast to currently approved technologies, LIFUP has the potential for noninvasive, yet highly targeted, neuromodulation. Multiple investigations have demonstrated neuromodulation with LIFUP in multiple animal models. Early demonstrations of low-

Address correspondence to: Alexander S. Korb, PhD, University of California, 300 UCLA Medical Plaza, 2335, Los Angeles, CA 90095, USA. Email: alexkorb@ucla.edu

* Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA;

† Department of Radiology, University of Southern California, Los Angeles, CA, USA; and

‡ Departments of Neurology, Radiology, Psychology, Biomedical Physics, and Bioengineering, University of California, Los Angeles, CA, USA

[Correction added after online publication 5-June 2013. In Materials and Methods section, linear radiofrequency amplifier corrected from model 403LA to 240L.]

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/bw/submit.asp?ref=1094-7159&site=1

Support: Support for this study came from Brainsonix, Inc. and the Gerald J. and Dorothy R. Friedman New York Foundation for Medical Research. Dr. Bystritsky provided the LIFUP device, courtesy of Brainsonix, Inc.

intensity focused US neuromodulation include stimulation of auditory nerve responses in cats (12). Another study showed that low-intensity continuous wave US could enhance nerve conduction in frogs (13). More recently, one group showed LIFUP capable of exciting neuronal circuits in mice, initially in excised brains (14) and then in live animals (15). Transcranial modulation of the hypothalamus also has been demonstrated in a mini-pig (2), the lower plate of the skull of which is very similar in thickness to the human temporal bone. Further research showed that the effects of LIFUP depend on US pulsing parameters (16). These experiments demonstrated that LIFUP is capable of either stimulating or suppressing regional cortical activity in rabbits *in vivo*. Most importantly for potential clinical applications, recent studies in rats demonstrate the remarkable result that LIFUP can reduce the duration and severity of seizures in both acute and chronic models of epilepsy (3,17).

Despite the therapeutic efficacy in animal models, the mechanism of LIFUP neuromodulation is not well characterized. It likely has an effect through mechanical interaction with neurons (18), and some speculate that this occurs via microtubules (19,20). And while the neuromodulatory effects of LIFUP have been demonstrated clearly in multiple animal models, it has not yet been tested in humans. LIFUP appears safe enough for human applications, as prior animal studies have examined sonicated tissue for evidence of ischemia, apoptosis, necrosis, and blood-brain barrier disruption and have not observed any noticeable tissue damage (14–16). This is not surprising given that LIFUP is effective even at intensities within the range of diagnostic US imaging (3,14,15). In consideration of the safety record of LIFUP in animal testing, once a suitable LIFUP device can be developed for human applications, human trials are warranted.

However, there are several challenges and possible safety concerns that must be addressed for this technique to be made ready for use in human subjects. First, for accurate targeting of LIFUP sonication, it is a practical necessity to use concurrent neuroimaging, such as that provided by magnetic resonance imaging (MRI). MRI is vital to positioning the transducer accurately, as the transducer can be moved in three dimensions. Functional MRI may also be used to visualize the effects of LIFUP on brain activity. Notably, the safety profile of a LIFUP device while utilized on a patient undergoing an MRI procedure has not yet been reported. MRI-related heating that may occur in association with the use of this equipment is a potential safety concern. The intent, in the present project, was to evaluate the MRI-related heating issues for a LIFUP device (BXPulsar 1001, Brainsonix, Inc., Los Angeles, CA, USA) by measuring heating of a skull sample during MRI.

Because the skull does not transmit US easily, another potential hazard is excessive heating caused by US absorption in the skull during sonication. Due to its limited aperture, this risk is increased in the case of a single-element transducer (21). Furthermore, while functional MRI scans that could be used concurrently with LIFUP have inherently low specific absorption rate (SAR), MR-related heating would be additive to US-related heating. Thus, we assessed heating of the skull sample during concurrent MRI with moderate SAR and LIFUP sonication as well.

MATERIALS AND METHODS

Phantom

MRI-related heating was assessed with a single-element transducer system (BXPulsar 1001, Brainsonix, Inc.) using an agar-substitute phantom prepared to simulate human brain tissue according to King et al. (22). This phantom was selected to simulate human brain tissue in thermal properties (at 20°C thermal conductivity = 0.55W/mC, diffusivity = 0.11 mm^2/sec), density (1.03 ± 0.02 g/cm^3), and absorption of US (at 20°C attenuation coefficient = $0.64f^{0.95}$ dB/cm, speed of sound = 1579 m/sec). Tissue-mimicking phantoms are used commonly for safety assessment of medical devices in MR environments, and this experimental setup was chosen in consideration of methodology described in previous reports (23–26).

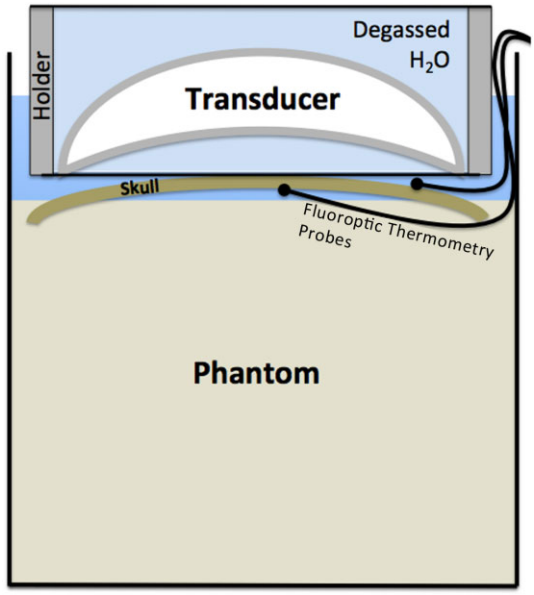

Figure 1. Diagram of experimental setup. This diagram represents a cross-section of the experimental setup. The skull sample and temperature probes were placed on top of the phantom and pressed lightly into it. The transducer holder, containing the transducer and degassed water, was placed on top of the skull sample. The rest of the container was filled with a 0.9% saline solution.

The phantom was created by mixing and heating calcium chloride (4 g), potassium sorbate (1 g), gellan gum powder (15 g), aluminum oxide powder (13.5 g), 1-propanol (120 mL), and degassed water (1 L), resulting in a hot gel. Approximately 980 mL of gel was allowed to equilibrate to room temperature in a 1.1 L plastic container. Once it cooled and solidified, a piece of human temporal bone (90 mm × 90 mm, Skulls Unlimited, Oklahoma City, OK, USA) was placed on top of the phantom and within the container (Fig. 1). To reduce the space between the skull sample and the phantom material, the skull sample was pressed gently into the phantom material. The rest of the container was then filled with a 0.9% saline solution. Because this phantom and experimental setup lack blood flow, this simulates an extreme condition used to assess MRI-related heating.

US System

The system consisted of an air-backed, spherical-segment focused US transducer (diameter = 6.1 cm; radius of curvature = 6.1 cm) operating at a fundamental frequency of 650 kHz (custom made by the University of Southern California Resource Center for Medical Ultrasonic Transducer Technology). The shape of the transducer resulted in a US beam that was focused at a distance equal to the radius of curvature. The transducer was controlled with a sinusoidal electrical signal from a function generator (Agilent Technology, Santa Clara, CA, USA), which was amplified by a linear radio-frequency (RF) amplifier (240L; ENI Inc., Rochester, NY, USA). The transducer was located in a plastic housing (Custom Stamping Inc., Carson City, NV, USA). The housing was filled with degassed, deionized water and enclosed with a polyethylene membrane permeable

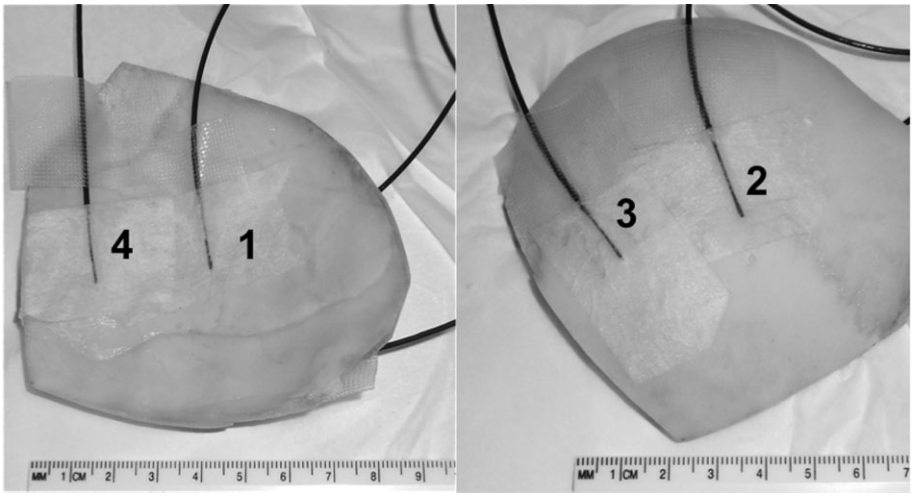

Figure 2. Probe placement. Placement of temperature probes on the top (Probe 1, Probe 4) and bottom (Probe 2, Probe 3) surfaces of the temporal bone sample. Probes captured temperature values every five seconds. Maximum temperature changes captured at these probes are listed in Table 2.

to US. The plastic housing contained an axial adjustment, which could raise and lower the transducer. In order to achieve the greatest potential for skull heating, the transducer was adjusted to maximal displacement from the skull, approximately 8 mm.

Temperature Measurements

Temperature measurements were obtained using a fluoroptic thermometry system (Model 3100, LumaSense Technologies, Santa Clara, CA, USA) with a laptop recording measurements every 5 sec. Fluoroptic thermometry probes (diameter 0.5 mm) were positioned on the skull to record temperatures during the heating assessment, as follows (Fig. 2):

1. Probe 1. Bottom surface of the skull beneath the center of the US transducer.
2. Probe 2. Top surface of the skull beneath the center of the US transducer.
3. Probe 3. Top surface of the skull beneath the edge of the US transducer.
4. Probe 4. Bottom surface of the skull beneath the edge of the US transducer.

Probes 2 and 3, being on top of the skull, were pressed between the skull and the membrane of the transducer holder. Probes 1 and 4, being beneath the skull, were pressed between the skull and the phantom. The positions for the thermometry probes were selected to study representative areas that would likely exhibit the highest temperatures during MRI-related and US-related heating scenarios. Probes were affixed to the surface of the skull with paper tape (3M Company, Minneapolis, MN, USA) known to be permeable to fluid and noninsulating. The probes were applied before the skull was submerged in saline as illustrated in Figure 2. The transducer, inside the holder, was placed at the midline of the phantom. The phantom was placed at the midline of the receive-only RF head coil (Fig. 3). The positions of the thermometry probes were inspected and verified immediately before and after the MRI-related heating assessment.

MRI and US Conditions

MRI was performed at 3 T/128 MHz (Siemens Medical, MAGNETOM Trio, software version VB17A, Erlangen, Germany) using a

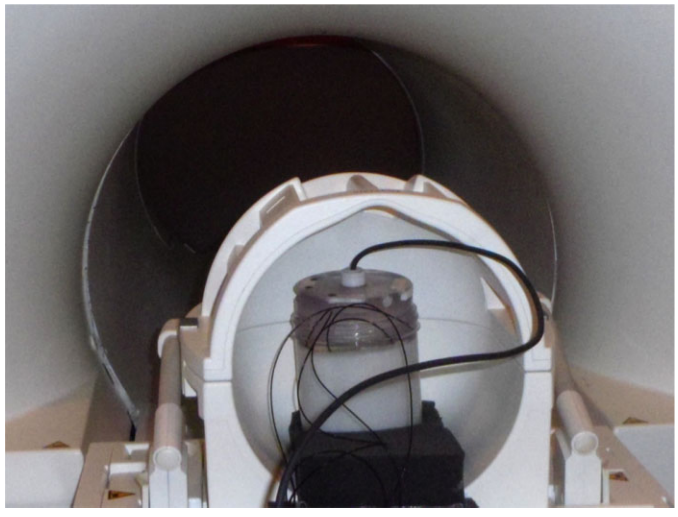

Figure 3. Phantom placement. Transducer was placed at midline of the phantom and phantom was placed at midline of the RF coil. The transducer connected by a coaxial cable to the penetration panel of the MR room and was driven by an amplifier and function generator. The leads to the temperature probes were connected to a fluoroptic temperature sensor.

12-channel receive-only RF head coil. MRI parameters were selected to utilize RF energy at either a medium (T2SPACE; TR = 3200; TE = 213; ETL = 141; slices = 15) or high level (Turbo Spin Echo; TR = 6100; TE = 79; ETL = 21; slices = 25) (27). A nominal weight of 120 lb was entered into the system. For the medium scan level, the MR system reported a whole-body average specific absorption rate (SAR) of 0.4 W/kg and a head average SAR of 1.1 W/kg. For the high-SAR scan, the MR system reported a whole-body average SAR of 0.7 W/kg and a head average SAR of 2.0 W/kg.

Two high-SAR scans were performed with no LIFUP sonication. Two medium-SAR scans were performed with LIFUP at the following parameters: pulse width = 0.5 msec, pulse repetition frequency = 100 Hz, derated spatial-peak temporal-average intensity (I_{spta}) = 3870m W/cm^2, and spatial-peak pulse-average intensity (I_{sppa}) = 77.4 W/cm^2. US intensities were derated from values measured in a water tank using an Onda HGL-1000 hydrophone (Onda Corp, Sunnyvale, CA, USA).

Table 1. Maximum Temperature Changes at Each Probe During MRI.

#	Head average SAR	US intensity (I_{spta})	Duration	Probe 1 ΔT (°C)	Probe 2 ΔT (°C)	Probe 3 ΔT (°C)	Probe 4 ΔT (°C)
1	2.0 W/kg	Off	520 sec	0.1	0.4	0.1	0.4
2	2.0 W/kg	Off	520 sec	0.1	0.5	0.0	0.6
3	1.1 W/kg	3870 mW/cm^2	520 sec	2.4	0.9	3.1	0.9
4	1.1 W/kg	3870 mW/cm^2	160 sec	1.7	0.6	2.3	0.6

The maximum temperature change from baseline is listed for each temperature probe in each of the four scans.
MRI, magnetic resonance imaging; SAR, specific absorption rate; US, ultrasound.

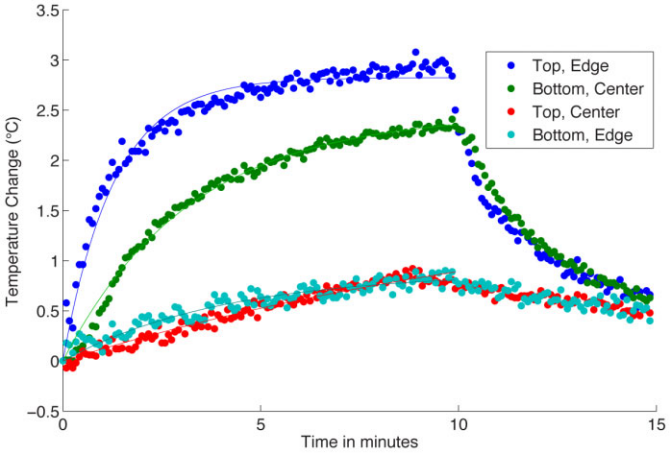

Figure 4. Heating due to LIFUP and medium SAR. Observed temperature changes are indicated by filled circles. Thin lines indicate curve fits to first-order kinetics. Probe 1 is shown in green (bottom, center), probe 2 in red (top, center), probe 3 in blue (top, edge), and probe 4 in light blue (bottom, edge).

RESULTS

The temperature-recording results are summarized in Table 1. These findings indicated that MRI-related heating in the high-SAR scan, without US applied, was very mild (≤0.6°C). In the medium-SAR scan, with LIFUP at a derated intensity of 3870 mW/cm^2, heating was substantially higher, though not at a level that would be dangerous for a human subject (Fig. 4). Temperature increase during LIFUP application in our experimental setup began rapidly but reached a plateau after approximately 7 min of continuous stimulation. The observed temperature decreases after LIFUP cessation was approximately symmetrical to the rate of increase. Quantitatively, this approximated an exponential time course fitted closely by the function

$$\theta = \theta_0\left(1-e^{-t/k}\right)$$

where θ indicates temperature, θ_0 is the final equilibrium temperature, and k is a time constant. Both θ_0 and k differed between probe locations (Table 2). These data and the small residual fitting errors suggest that only uncomplicated first-order temperature kinetics are needed for accurate modeling of final tissue temperature in essentially arbitrary patterns of LIFUP application. Because LIFUP in clinical use will be limited to under 30 sec per sonication application, the maximal heating over the first 30 sec is shown in Table 3. Both the experimental data and the model indicate maximum temperature increases of less than 1°C.

Table 2. Estimated Heating Parameters.

Location	θ_0 (°C)	k (sec)	r.m.s. fit error
Top, Edge	2.83	78	0.0130°
Bottom, Center	2.47	193	0.0046°
Top, Center	1.75	840	0.0029°
Bottom, Edge	0.88	243	0.0045°

These are the best fit estimates to the equation $\theta = \theta_0(1 - e^{-t/k})$, where θ indicates temperature, θ_0 is the final equilibrium temperature, and k is a time constant.

DISCUSSION

The highest temperature increase recorded for the LIFUP device during MRI performed at a relatively high, head-averaged SAR (2.0 W/kg) was 0.6°C. This slight temperature change is not a safety concern for human subjects. This finding is not surprising given that the transducer and holder contain no metal other than the insulated input cable and a small amount of solder. In addition, no metal touches the phantom (nor will metal be in contact with the patient during the intended use of this device). Therefore, MRI-related heating is not of concern for this particular device.

Under the MRI conditions used in this evaluation, the findings indicated that the LIFUP device is safe from a thermal perspective, as evidenced by minimal heating, even at high SAR level. Typical clinical procedures performed at 3 T/128 MHz use even lower SAR levels, and thus, MRI-related heating will be even less.

Not surprisingly, given that the skull is known to absorb US, greater heating was observed during LIFUP sonication. The heating was quite moderate, with a maximum temperature change at any thermometry probe of only 3.1°C. However, this was observed only after more than 8 min of continual use. Importantly, therapeutic LIFUP is intended for only brief applications (e.g., under 30 sec). Heating in the short term was dramatically lower than heating over several minutes. Over the course of the first 30 sec, the greatest temperature rise observed at any thermometry probe was still below 1°C. Obviously, lower intensities of LIFUP have even lower risk of heating.

The heating behavior was consistent with the deposition of constant heat energy into a thermal reservoir of fixed capacity and constant cooling rate. The amount of heating and time course varied by the location of each thermometry probe. This is likely due to numerous factors including variability of skull thickness and the angle of the skull relative to the US transducer, which can affect US absorption. In addition, there may also have been additional artifactual heating caused by tiny air bubbles trapped by the skull or tape; these have the potential to increase US heating. In the clinical setting, air bubbles will not be present, as LIFUP will be applied

Table 3. Maximum Temperature Changes From 30 Sec of Sonication.

#	Head average SAR	US intensity (I_{spta})	Probe 1 ΔT (°C)	Probe 2 ΔT (°C)	Probe 3 ΔT (°C)	Probe 4 ΔT (°C)
1	1.1 W/kg	3870 mW/cm^2	0.2	0.1	1.0	0.3
2	1.1 W/kg	3870 mW/cm^2	0.0	0.2	0.8	0.2

The maximum temperature change from baseline experienced at each temperature probe during the first 30 sec of simultaneous LIFUP and MRI. For therapeutic clinical applications, LIFUP is intended to be used for durations of 30 sec or less per sonication.
LIFUP, low-intensity focused ultrasound pulsation; SAR, specific absorption rate; US, ultrasound.

through the unopened skin and skull. Furthermore, several studies have shown that, owing to perfusion, US heating is lower in live tissue than cadaveric tissue by 25–43% (28,29). Given the use of a static phantom material, which lacks perfusion, it can be presumed that *in vivo* human applications present an even lower risk of heating. This experimental setup, therefore, represents a worst-case scenario.

Tissue safety during temperature increases is related to both the magnitude and duration of the applied heat (30,31). The clinically accepted time of safe exposure to temperature increases is described by the equation $T_s = 4^{6-t}$, where T_s is the length of time, in minutes, of safe heating and t is steady-state temperature change. The equation states that an increase of 3°C, for example, is safe for a 64-min period of application. In the experiments performed in this investigation, temperature increases on the interior surface of the skull stayed below 1°C for the first 30 sec. Therefore, LIFUP used for periods shorter than 30 sec is unlikely to cause any thermal damage.

The safety of the LIFUP device relative to the concomitant use of MRI, especially when performed at 3 T/128 MHz, is crucial for applications to human subjects. Because the US beam may be deflected by the skull, concurrent use of LIFUP and MRI is a practical necessity to determine whether LIFUP sonication is reaching and/or affecting the target brain region. In the future, it may be possible to use MRI only in an initial examination for LIFUP targeting and, once targeting parameters have been determined, perform subsequent LIFUP procedures without an MRI.

LIFUP presents the possibility of the same neuromodulatory capabilities as DBS, but without surgery. DBS has shown promise in the treatment of numerous disorders, including chronic pain, epilepsy, obsessive–compulsive disorder, depression, obesity, and many other applications (4,5,32,33). Thus, all these disorders are potential treatment targets for LIFUP. Therapy with LIFUP may be most appropriate when medical treatments alone are not adequate and when invasive strategies (i.e., ablation and DBS) are not appropriate. An added advantage of LIFUP is that, by coupling it with fMRI, malfunctioning neuronal circuits participating in the pathophysiology of these illnesses could potentially be correctly identified and probed prior to treatment.

No discussion of LIFUP would be complete without contrasting it with magnetic resonance guided high-intensity focused US (MRg-HIFU), which is currently being used in human trials for a variety of clinical applications, including neuropathic pain (34) and essential tremor (35). There are several differences between MRg-HIFU and LIFUP that provide insight into the safety profile of LIFUP. Most importantly, MRg-HIFU uses very high-intensity continuous US to heat tissue, generally more than ten times the intensities used here and often much greater. In contrast, LIFUP uses low-intensity US in a pulsed manner, which greatly reduces the likelihood of heating in the tissue. The main source of risk for LIFUP comes from the limited aperture of a single-element transducer, which increases the risk of skull heating. Addressing this risk is one of the primary reasons we performed this study. Lastly, phased arrays in MRg-HIFU allow for shaping of the US focus, which can be distorted and displaced by the skull. A single-element transducer presents a challenge in creating a well-defined focus through the skull. LIFUP is therefore confined mostly to targets beneath the thin temporal window. However, by using a low frequency and by targeting through the thin temporal bone, even a single-element transducer can result in a well-formed focus (36).

LIMITATIONS

While these results indicate that concurrent use of LIFUP and MRI will not cause excessive heating of the skull, this is not a definitive test of LIFUP safety. In addition to skull heating, US has the potential also to heat brain tissue. However, the methods used in this paper do not address this issue.

It is possible that higher temperature increases occurred not on the surface of the skull, but within the bone itself. However, physical and practical limitations prevent placement of temperature probes within the thin temporal bone to make accurate, nonartifactual measurements. Furthermore, as the heat does not have very far to diffuse to the surface, the temperature probes would still be able to detect its effects.

CONCLUSIONS

Importantly, the findings reported herein are highly specific to the MRI conditions that were used in our investigation. MRI-related heating will require further characterization if a different static magnetic field strength/RF frequency is used and/or if a transmit/receive head coil is utilized for the MRI examination. Given that it creates only mild heating of the skull during typical clinical use conditions, LIFUP appears to be safe for applications in human subjects with concurrent MRI performed at 3 T/128 MHz. Therefore, we propose to initiate first-in-human trials of LIFUP in the near future.

Authorship Statement

All authors contributed to the design of the study. Dr. Cohen prepared the MR pulse sequences and performed the analytic temperature modeling. Dr. Korb prepared the phantom and, along with Dr. Shellock, collected the data. Dr. Korb prepared the manuscript draft with important intellectual input from Drs. Shellock, Cohen, and Bystritsky. All authors approved the final manuscript. All authors had complete access to the study data.

How to Cite this Article:

Korb A.S., Shellock F.G., Cohen M.S., Bystritsky A. 2014. Low-Intensity Focused Ultrasound Pulsation Device Used During Magnetic Resonance Imaging: Evaluation of Magnetic Resonance Imaging-Related Heating at 3 Tesla/128 MHz.
Neuromodulation 2014; 17: 236–241

REFERENCES

1. Bystritsky A, Korb AS, Douglas PK et al. A review of low-intensity focused ultrasound pulsation. *Brain Stimul* 2011;4:125–136.
2. Mulgaonkar AP, Singh RS, Babakhanian M et al. A prototype stimulator system for noninvasive low intensity focused ultrasound delivery. *Stud Health Technol Inform* 2012;173:297–303.
3. Min BK, Bystritsky A, Jung KI et al. Focused ultrasound-mediated suppression of chemically-induced acute epileptic EEG activity. *BMC Neurosci* 2011;12:23.
4. Taghva AS, Malone DA, Rezai AR. Deep brain stimulation for treatment resistant depression. *World Neurosurg* 2013, in press.
5. Yeremeyeva E, Taghva A, Rezai AR. Seeking new solutions: stimulation of diseased circuits in depression and other neurobehavioral disorders. *Clin Neurosurg* 2012;59:44–49.
6. Swann N, Poizner H, Houser M et al. Deep brain stimulation of the subthalamic nucleus alters the cortical profile of response inhibition in the beta frequency band: a scalp EEG study in Parkinson's disease. *J Neurosci* 2011;31:5721–5729.
7. Cheung SW, Larson PS. Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area LC). *Neuroscience* 2010;169:1768–1778.
8. Beric A, Kelly PJ, Rezai A et al. Complications of deep brain stimulation surgery. *Stereotact Funct Neurosurg* 2001;77:73–78.
9. George MS, Sackeim HA, Rush AJ et al. Vagus nerve stimulation: a new tool for brain research and therapy. *Biol Psychiatry* 2000;47:287–295.
10. Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–2039.
11. Parazzini M, Fiocchi S, Rossi E, Paglialonga A, Ravazzani P. Transcranial direct current stimulation: estimation of the electric field and of the current density in an anatomical human head model. *IEEE Trans Biomed Eng* 2011;58:1773–1780.
12. Foster KR, Wiederhold ML. Auditory responses in cats produced by pulsed ultrasound. *J Acoust Soc Am* 1978;63 (S1):S27–S28.
13. Tsui PH, Wang SH, Huang CC. In vitro effects of ultrasound with different energies on the conduction properties of neural tissue. *Ultrasonics* 2005;43:560–565.
14. Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. *Plos ONE* 2008;3:e3511.
15. Tufail Y, Matyushov A, Baldwin N et al. Transcranial pulsed ultrasound stimulates intact brain circuits. *Neuron* 2010;66:681–694.
16. Yoo SS, Bystritsky A, Lee JH et al. Focused ultrasound modulates region-specific brain activity. *Neuroimage* 2011;56:1267–1275.
17. Yoo SS, Jung KI, Zhang Y, McDannold N, Bystritsky A, Jolesz F. Non-invasive suppression of animal-model chronic epilepsy using image-guided focused ultrasound. Stockholm: Paper presented at SMRM-ESMRMB Joint Annual Meeting, 2010.
18. Dalecki D. Mechanical bioeffects of ultrasound. *Annu Rev Biomed Eng* 2004;6:229–248.
19. Hameroff S, Trakas M, Duffield C et al. Transcranial ultrasound (TUS) effects on mental states: a pilot study. *Brain Stimul* 2013, in press.
20. Pokorny J. Excitation of vibrations in microtubules in living cells. *Bioelectrochemistry* 2004;63:321–326.
21. Sun J, Hynynen K. Focusing of therapeutic ultrasound through a human skull: a numerical study. *J Acoust Soc Am* 1998;104 (3 Pt 1):1705–1715.
22. King RL, Liu Y, Maruvada S, Herman BA, Wear KA, Harris GR. Development and characterization of a tissue-mimicking material for high-intensity focused ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control* 2011;58:1397–1405.
23. Shellock FG, Habibi R, Knebel J. Programmable CSF shunt valve: in vitro assessment of MR imaging safety at 3T. *AJNR Am J Neuroradiol* 2006;27:661–665.
24. Shellock FG, Wilson SF, Mauge CP. Magnetically programmable shunt valve: MRI at 3-Tesla. *Magn Reson Imaging* 2007;25:1116–1121.
25. Shellock FG, Begnaud J, Inman DM. Vagus nerve stimulation therapy system: in vitro evaluation of magnetic resonance imaging-related heating and function at 1.5 and 3 tesla. *Neuromodulation* 2006;9:204–213.
26. Shellock FG, Crivelli R, Venugopalan R. Programmable infusion pump and catheter: evaluation using 3-tesla magnetic resonance imaging. *Neuromodulation* 2008;11:163–170.
27. Shellock FG, Valencerina S. In vitro evaluation of MR imaging issues at 3T for aneurysm clips made from MP35N: findings and information applied to 155 additional aneurysm clips. *AJNR Am J Neuroradiol* 2010;31:615–619.
28. Horder MM, Barnett SB, Vella GJ, Edwards MJ. Effects of pulsed ultrasound on sphenoid bone temperature and the heart rate in guinea-pig foetuses. *Early Hum Dev* 1998;52:221–233.
29. Duggan PM, Liggins GC, Barnett SB. Ultrasonic heating of the brain of the fetal sheep in utero. *Ultrasound Med Biol* 1995;21:553–560.
30. Miller MW, Ziskin MC. Biological consequences of hyperthermia. *Ultrasound Med Biol* 1989;15:707–722.
31. NCRP. Exposure criteria for medical diagnostic ultrasound: criteria based on thermal mechanism. Bethesda, MD: National Council of Radiation Protection and Measurements, 1992. Report No. 113.
32. Oluigbo CO, Salma A, Rezai AR. Targeting the affective and cognitive aspects of chronic neuropathic pain using basal forebrain neuromodulation: rationale, review and proposal. *J Clin Neurosci* 2012;19:1216–1221.
33. Taghva A, Corrigan JD, Rezai AR. Obesity and brain addiction circuitry: implications for deep brain stimulation. *Neurosurgery* 2012;71:224–238.
34. Jeanmonod D, Werner B, Morel A et al. Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurg Focus* 2012;32:E1.
35. Elias JW, Huss D, Khaled MA et al. MR-guided focused ultrasound lesioning for the treatment of essential tremor. A new paradigm for noninvasive lesioning and neuromodulation. Washington, DC: Paper presented at Congress of Neurological Surgeons Annual Meeting, 2011.
36. Hynynen K, Jolesz F. Demonstration of potential noninvasive ultrasound brain therapy through an intact skull. *Ultrasound Med Biol* 1998;24:275–283.

COMMENTS

High intensity focused ultrasound has recently been introduced as a method for producing precise lesions in the brain under MRI control. This technology is currently being evaluated for the treatment of essential tremor and chronic pain, and may have other applications for the treatment of neurological diseases. The complex problem of focusing ultrasound waves through the skull to precisely affect deep brain structures therefore appears to be tractable. This manuscript provides the results of initial safety testing for a low-intensity focused ultrasound system, which could have the potential for modulation rather than lesioning of deep brain structures. Using a non-invasive method to probe neural circuitry while monitoring both behavioral and imaging correlates has obvious implications for the understanding and treatment of many poorly understood neurological disorders.

To the extent that the authors evaluated this device, it appears relatively safe to use in an MRI environment. However, there are still unanswered questions regarding deep heating, which would be best answered using a technique such as MR thermography. Given the safety record currently being established for high-intensity focused ultrasound, it seems likely that the low-intensity regime will prove equally well tolerated. I look forward to seeing further studies on the use of this technology for non-invasive neuromodulation.

Jaimie Henderson, MD
Stanford, CA, USA

***

This paper provides evidence of safe energy deposition during MRI-guided US mediated neuromodulation by proving that no significant skull heating occurs.

Ferenc Jolesz, MD
Boston, MA, USA

Comments not included in the Early View version of this paper.

