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● *Original Contribution*

EXPERIMENTAL METHODS FOR IMPROVED SPATIAL CONTROL OF THERMAL LESIONS IN MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND ABLATION

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Abstract—Magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU, or MRgFUS) is a hybrid technology that was developed to provide efficient and tolerable thermal ablation of targeted tumors or other pathologic tissues, while preserving the normal surrounding structures. Fast 3-D ablation strategies are feasible with the newly available phased-array HIFU transducers. However, unlike fixed heating sources for interstitial ablation (radiofrequency electrode, microwave applicator, infra-red laser applicator), HIFU uses propagating waves. Therefore, the main challenge is to avoid thermo-acoustical adverse effects, such as energy deposition at reflecting interfaces and thermal drift of the focal lesion toward the near field. We report here our investigations on some novel experimental solutions to solve, or at least to alleviate, these generally known tolerability problems in HIFU-based therapy. Online multiplanar MR thermometry was the main investigational tool extensively used in this study to identify the problems and to assess the efficacy of the tested solutions. We present an improved method to cancel the beam reflection at the exit window (i.e., tissue-to-air interface) by creating a multilayer protection, to dissipate the residual HIFU beam by bulk scattering. This study evaluates selective de-activation of transducer elements to reduce the collateral heating at bone surfaces in the far field, mainly during automatically controlled volumetric ablation. We also explore, using hybrid US/MR simultaneous imaging, the feasibility of using disruptive boiling at the focus, both as a far-field self-shielding technique and as an enhanced ablation strategy (*i.e.,* boiling core controlled HIFU ablation). (E-mail: magalie.viallon@hcuge.ch) © 2013 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Magnetic resonance-guided high-intensity focused ultrasound, Cavitation, Boiling core, Safety profile, Targeting, Pre-clinical quality assurance.**

INTRODUCTION

Magnetic resonance (MR)-guided high-intensity focused ultrasound (MRgHIFU, or MRgFUS) is a hybrid technology that provides efficient and tolerable thermal ablation of predefined tumoral volumes and other pathologic tissues, while leaving the surrounding healthy structures unaltered (Jolesz 2009).

The use of high-intensity focused ultrasound (HIFU, or FUS) to produce local lesions is already well established (Fry et al. 1954; Lele 1962; Lynn et al. 1942). The development of MR-compatible US transducers and electronics in combination with MR thermometry was first proposed by Cline et al. (1992) and allowed, for the first time, the monitoring of thermal ablation progress during sonication (Cline et al. 1992, 1995). Aside from the monitoring of thermal effects, another modality for MR guidance of HIFU is acoustic radiation force imaging (McDannold and Maier 2008; Souchon et al. 2008).

Phased-array HIFU transducers can concentrate multiple coherent elementary ultrasonic beams with sub-millimeter precision on a target tissue, but can also create large thermal lesions by using continuous sonication and volumetric sweeping (Salomir et al. 2000, 2006; Hokland et al. 2006).

Although the highest temperature elevation induced by the HIFU beam is expected to occur around the focal point, every penetrated tissue on the pathway of the wave (in front of or behind the focus) is also heated to various levels depending on acoustic and physiologic properties

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and on its relative position from the transducer. Thermal buildup may occur, for example, in the near and far field of the transducer (typically the skin) as a result of repeated exposure to low-intensity and spatially smooth acoustic fields, and the situation is worsened in the presence of reflective interfaces. In the near field, pre-focal phenomena such as cavitation, boiling and thermally enhanced absorption may induce thermal drift of the ablative lesion toward the transducer.

Such conditions justify "point-by-point" treatments, sequentially cumulating independent and small thermal lesions that are temporally separated by delays sufficient to allow tissue cooling. InSightec's ExAblate 2000/2100 is the only U.S. Food and Drug Administration-approved MRgHIFU device for treatment of benign uterine fibroids. The "point-by-point" sonication, jointly used with proton resonance frequency shift (PRFS) MR thermometry reference reset after cooling, is the primary method clinically investigated to date to treat malignant tumors off-label (Gianfelice et al. 2003a, 2003b, 2003c, 2008; Huber et al. 2001a, 2001b; Hynynen et al. 1995, 2001a, 2001b, 2006). The current treatment duration range is several hours (Furusawa et al. 2006; Gianfelice et al. 2008). This tends to make the procedure both expensive and uncomfortable for the patient, potential obstacles to the widespread use of MRgHIFU. Moreover, the "point-by-point" approach appears sub-optimal for malignant tumors because the ablation zone may not be uniform enough to ensure that no malignant cells remain alive.

Fast volumetric ablation (Palussiere et al. 2003) has been investigated *in vivo* and has been reported to achieve a large and uniform ablation zone rapidly. However, a high thermal contrast must be ensured between the focal lesion and the secondary thermal buildup in the near or far field, with no damage at reflective interfaces (*e.g.,* air/tissue for skin or bowel or soft tissue/bone). Indeed, studies have tentatively addressed the problem of side effects in the near field (*e.g.,* reflection at the ribs [Civale et al. 2006; Quesson et al. 2010; Salomir et al. 2013]), but no solutions have yet been presented for side effects in the far field.

To improve the accuracy and spatial control of ablation, with the goal of more tolerable HIFU ablation, several potential solutions were evaluated in this study: (i) multilayer protection to cancel air/tissue reflection and prevent skin burning at the exit acoustic window; (ii) selective de-activation of transducer elements to reduce bone heating in the far field during automatically controlled volumetric ablation; (iii) disruptive boiling both as a far-field self-shielding technique and as an enhanced ablation strategy. Three-dimensional high-resolution anatomic MR imaging (MRI), online multiplanar high-resolution PRFS-based MR thermometry (MRT) (Ishihara et al. 1995; Peters et al. 1999; Rempp et al. 2008) and, per need, simultaneous MR/ultrasonography hybrid imaging were the main investigational tools extensively used in this study, *ex vivo* and *in vivo*, to identify safety profile problems and to assess the efficacy of the tested solutions.

METHODS

High-intensity focused ultrasound system

Ex vivo and *in vivo* MRgHIFU experiments were conducted using a randomly assigned 256-element phased-array transducer (Imasonic, Besançon, France) operating in the frequency range 974 to 1049 kHz, with a natural focal length and aperture of $R = 130$ mm and $D = 140$ mm (aperture number $D/R = 1.077$), respectively. The HIFU platform uses a programmable 256-channel generator and a 2-D positioning mechanism in the horizontal (xz) plane (both from Image Guided Therapy, Pessac, France). Each channel delivers a radiofrequency sine wave, with independent control of the phase, frequency and amplitude. Electronic steering of the focal point was available within a –3-dB revolution ellipsoid of axes 30, 30 and 50 mm around the natural focus. The update of phase and amplitude for the 256 channels takes less than 10 ms, and the focal point position could be changed 20 times per second to follow any complex trajectory. The delivered power was monitored on-line, as the forward and reflected electrical powers were measured continuously. The positioning mechanism for the transducer provides two independent horizontal translation axes, that is, x and z in the magnet frame, within a displacement range of ± 80 mm in each direction with 0.5-mm accuracy. The maximum available acoustic power was 240 W peak and 200 W mean. In-house written software packages for real-time treatment planning and hardware control supplemented the graphical user interface (Thermoguide, Image Guided Therapy, Pessac, France). The software interface displayed real-time temperature maps and provided automatic feedback control of temperature evolution during volumetric sonication.

US MRI-compatible system

Simultaneous ultrasound imaging was achieved using an Acuson clinical ultrasound scanner (Antares, Siemens Medical Solutions, Mountain View, CA, USA) equipped with abdominal imaging packages (real-time image reconstruction and display), B-mode, pulse train, low energy, color Doppler mode and tissue harmonic imaging (ITH). Moreover, the system is equipped with an ultrasound contrast agent (UCA) imaging pulse sequence (Raisinghani et al. 2004; Rofsky et al. 1999). The CH4–1 imaging probe (256-element phase-array