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● *Original Contribution*

MAGNETIC RESONANCE IMAGING FOR THE EXPLOITATION OF BUBBLE-ENHANCED HEATING BY HIGH-INTENSITY FOCUSED ULTRASOUND: A FEASIBILITY STUDY IN *EX VIVO* LIVER

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Abstract—Bubble-enhanced heating (BEH) may be exploited to improve the heating efficiency of high-intensity focused ultrasound in liver and to protect tissues located beyond the focal point. The objectives of this study, performed in *ex vivo* pig liver, were (i) to develop a method to determine the acoustic power threshold for induction of BEH from displacement images measured by magnetic resonance acoustic radiation force imaging (MR-ARFI), and (ii) to compare temperature distribution with MR thermometry for HIFU protocols with and without BEH. The acoustic threshold for generation of BEH was determined in *ex vivo* pig liver from MR-ARFI calibration curves of local tissue displacement resulting from sonication at different powers. Temperature distributions (MR thermometry) resulting from "conventional" sonications (20 W, 30 s) were compared with those from "composite" sonications performed at identical parameters, but after a HIFU burst pulse (0.5 s, acoustic power over the threshold for induction of BEH). Displacement images (MR-ARFI) were acquired between sonications to measure potential modifications of local tissue displacement associated with modifications of tissue acoustic characteristics induced by the burst HIFU pulse. The acoustic threshold for induction of BEH corresponded to a displacement amplitude of approximately 50 μm in *ex vivo* liver. The displacement and temperature images of the composite group exhibited a nearly spherical pattern, shifted approximately 4 mm toward the transducer, in contrast to elliptical shapes centered on the natural focal position for the conventional group. The gains in maximum temperature and displacement values were 1.5 and 2, and the full widths at half-maximum of the displacement data were 1.7 and 2.2 times larger than in the conventional group in directions perpendicular to ultrasound propagation axes. Combination of MR-ARFI and MR thermometry for calibration and exploitation of BEH appears to increase the efficiency and safety of HIFU treatment. (E-mail: delphine.elbes@gmail.com) © 2014 World Federation for Ultrasound in Medicine & Biology.

Key Words: **High-intensity focused ultrasound, Magnetic resonance imaging, Magnetic resonance thermometry, Magnetic resonance acoustic radiation force imaging, Bubble-enhanced heating, Acoustic cavitation, Boiling.**

INTRODUCTION

Thermal ablation with high-intensity focused ultrasound (HIFU) is being used increasingly for the non-invasive treatment of malignant tumors (Chapman and ter Haar 2007; Enholm et al. 2010; Kim et al. 2010; Quesson et al. 2010). Magnetic resonance (MR) thermometry allows on-line monitoring of the procedure, control of the heating sonication in real time (Quesson et al. 2011), estimation of the localization of the focus and prediction of thermal lesion size through calculation of the accumulated thermal dose (Sapareto and Dewey 1984). Different sonication strategies developed to enlarge thermal lesions are based on continuous sonication with electronic deflection and the design of trajectories including thermal diffusion phenomenon to create large and homogeneous ablation volumes while reducing the energy required (Köhler et al. 2009; Mougenot et al. 2004), compared with point-by-point sonication. The presence of a bubble cloud in the medium can be used to enlarge the heated region near the focal point by modifying the spatial distribution of the acoustic intensity (Hynynen 1991; Sokka et al.

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2003; Vanhille and Campos-Pozuelo 2009), resulting in a "tadpole" shape. Sokka et al. (2003) proposed generation of acoustic cavitation *in situ* at the focal point, including a burst pulse at the beginning of the sonication protocol. The advantages of this method are: generation of a nearly spherical lesion, an increase in the maximal temperature rise and shielding of the ultrasound beam beyond the natural focal point by the bubble cloud or layer (Vanhille and Campos-Pozuelo 2009). The last advantage may thus help in reducing the risk of damage to tissues located in the far field (Zderic et al. 2008).

Although HIFU heating in the presence of acoustic cavitation appears advantageous for increasing heating efficiency, its applicability *in vivo* is limited because of difficulty in precisely controlling the phenomenon. Local acoustic pressure has to reach a threshold to induce cavitation. Local intensity at the targeted area appears hardly predictable because of potential acoustic wave aberrations and absorption as the ultrasound beam passes through inhomogeneous structures (skin, subcutaneous fat layers, bones, bowels).

In Sokka and colleagues' (2003) experiments, the acoustic threshold was detected by analyzing the backward acoustic spectrum caused by bubble activity (Hynynen 1991; Lele 1967). More recently, acoustic mapping of broadband and harmonic emissions (Jensen et al. 2012) was proposed to improve this technique. However, the analysis of such a signal, for the treatment of liver tumors, may be complicated by signal attenuation and scattering. Khokhlova et al. (2009) reported that boiling may be the main cause of bubble (Khokhlova et al. 2006) generation. Irrespective of the physical cause of local changes in the acoustic properties of tissues, the resulting lesion and heating pattern remain similar in terms of shape and localization (shift toward the transducer). Furthermore, this change, related to bubble-enhanced heating (BEH), could be correlated with an acoustic power threshold. In addition to already established applications of magnetic resonance acoustic radiation force imaging (MR-ARFI) (Kaye et al. 2011; Larrat et al. 2010; Marsac et al. 2012), this non-invasive imaging method appears to be a suitable candidate to investigate focal patterns of ultrasound distribution through images of local tissue displacement in the range of a few micrometers induced by HIFU pulses, and limits the risks of unwanted thermal damage through use of low-duty-cycle ultrasound pulses (Chen et al. 2010; McDannold and Maier 2008; Sinkus et al. 2008).

The objectives of this study performed in *ex vivo* pig liver were: (i) to develop a method to determine the acoustic power threshold for induction BEH from displacement images measured by MR-ARFI, and (ii) to compare temperature distributions with MR thermometry for HIFU sonication protocols performed with and without BEH.

METHODS

Experimental setup

Experiments were performed at 1.5 T with the Sonalleve MR-HIFU platform (Fig. 1) (Philips Healthcare, Vantaa, Finland) designed for the treatment of uterine fibroids (see Köhler et al. [2009] for a technical description of the device). All sonications were performed at a frequency of 1.2 MHz in *ex vivo* porcine liver samples (N = 6, fresh piece of pig liver, not degassed, purchased from butcher, used within the day of delivery from the butcher) at room temperature. The liver was immersed in degassed water in a cylindrical plastic tank (20 cm in diameter) equipped with a membrane at the bottom. This holder was positioned on top of the platform at the center of the acoustic window. A mixture of ultrasonic gel and degassed water was applied between the two membranes (one at the bottom of the holder, one at the acoustic window of the HIFU platform) to ensure acoustic coupling. MR images were acquired with a circular single-element surface coil located on top of the cylindrical container.

MR-ARFI measurements

The MR-ARFI acquisition sequence was a modified spin-echo sequence. Two motion-sensitive bipolar gradients were added symmetrically from the refocusing pulse.

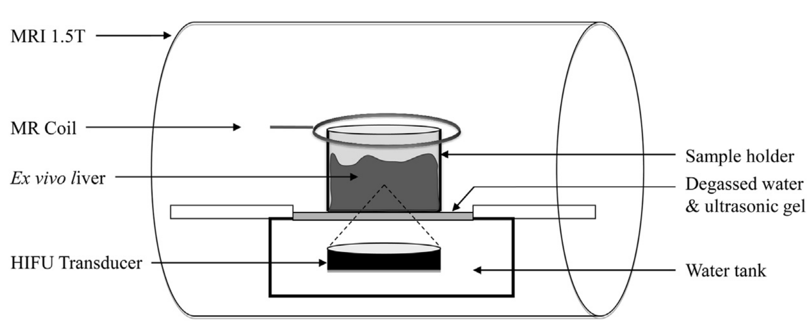

Fig. 1. Experimental setup of magnetic resonance imaging (MRI)-guided high-intensity focused ultrasound (HIFU) of *ex vivo* pig liver for the exploitation of bubble-enhanced heating.