Ultrasonics - Sonochemistry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Ultrasonics - Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

The enhanced HIFU-induced thermal effect via magnetic ultrasound contrast agent microbubbles

Dongxin Yang[a], Zhengyang Ni[a], Yanye Yang[a], Guangyao Xu[a], Juan Tu[a,*], Xiasheng Guo[a], Pintong Huang[b], Dong Zhang[a,c,*]

[a] Key Laboratory of Modern Acoustics (MOE), Department of Physics, Collaborative Innovation Center of Advanced Microstructure, Nanjing University, Nanjing 210093, China

[b] Department of Ultrasound, The Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou 310009, China

[c] The State Key Laboratory of Acoustics, Chinese Academy of Science, Beijing 10080, China

ARTICLE INFO

Keywords:
Super paramagnetic iron oxide nanoparticles
Microbubbles
HIFU-induced thermal effect
Cavitation activity

ABSTRACT

High intensity focused ultrasound (HIFU) has been regarded as a promising technology for treating cancer and other severe diseases noninvasively. In the present study, dual modality magnetic ultrasound contrast agent microbubbles (MBs) were synthesized by loading the super paramagnetic iron oxide nanoparticles (SPIOs) into the albumin-shelled MBs (referred as SPIO-albumin MBs). Then, both experimental measurements and numerical simulations were performed to evaluate the ability of SPIO-albumin MBs of enhancing HIFU-induced thermal effect. The results indicated that, comparing with regular albumin-shelled MBs, the SPIO-albumin MBs would lead to quicker temperature elevation rate and higher peak temperature. This phenomenon could be explained by the changes in MBs' physical and thermal properties induced by the integration of SPIOs into MB shell materials. In addition, more experimental results demonstrated that the enhancement effect on HIFU-induced temperature elevation could be further strengthened with more SPIOs combined with albumin-shell MBs. These observations suggested that more violent cavitation behaviors might be activated by ultrasound exposures with the presence of SPIOs, which in turn amplified ultrasound-stimulated thermal effect. Based on the present studies, it is reasonable to expect that, with the help of properly designed dual-modality magnetic MBs, the efficiency of HIFU-induced thermal effect could be further improved to achieve better therapeutic outcomes.

1. Introduction

High intensity focused ultrasound (HIFU)-induced thermal effect is a promising tool for cancer therapy that is capable to achieve cancer treatment in selected regions [1–7]. Meanwhile, HIFU has also been widely used in hemorrhage control [8], blood-brain-barrier opening [9], and drug/gene delivery [10]. Considering the energy loss caused by convective heat transfer in the tissue, higher ultrasound intensity and longer treatment time are often adopted, which might cause unexpected damage to the tissue nearby [11]. Many studies have shown that adding contrast agent MBs can improve the HIFU-induced thermal effect because of the interaction between ultrasound and MBs, which is helpful for reducing the adopted ultrasound intensity and exposure time [4,12,13].

Nonlinear vibration and cavitation may happen when MBs are driven by ultrasound, which tend to increase the local absorption of acoustical energy [14]. The viscous damping causes part of the bubbles' mechanical energy to be converted into thermal energy, thus heating the surrounding medium, i.e., enhancing the thermal effect of HIFU [15–18]. The viscous dissipation of encapsulated MBs is much higher than free ones, due to the viscous friction between the surrounding liquid and the coating material [19–21]. Furthermore, increasing the concentration of MB can improve the enhancement effect of MBs on HIFU-induced thermal effect. However, due to the shielding effect of MBs, lesion migration and uncontrollable injury might be induced when the concentration gets to be too high [16,18,22]. Therefore, urgent demand still exists for the optimization of MBs that can enhance HIFU-induced thermal effect with higher efficiency.

In the present work, dual modality magnetic ultrasound contrast agent MBs were fabricated by embedding super paramagnetic iron oxide nanoparticles (SPIOs) into albumin-shelled MBs (referred as SPIO-albumin MBs), with facile surface modification, the presence of

* Corresponding authors at: Key Laboratory of Modern Acoustics (MOE), Department of Physics, Collaborative Innovation Center of Advanced Microstructure, Nanjing University, Nanjing 210093, China (D. Zhang).
E-mail addresses: juantu@nju.edu.cn (J. Tu), dzhang@nju.edu.cn (D. Zhang).

https://doi.org/10.1016/j.ultsonch.2018.07.031
Received 10 May 2018; Received in revised form 6 July 2018; Accepted 23 July 2018
1350-4177/

Please cite this article as: Yang, D., Ultrasonics - Sonochemistry (2018), https://doi.org/10.1016/j.ultsonch.2018.07.031

SPIOs in MB shell provides enough acoustic and magnetic susceptibility to accomplish superb ultrasound (US) and magnetic resonance (MR) detectability and sensitivity [23]. Our previous studies have shown that the physical properties (e.g., size distribution and shell parameters), acoustic attenuation response, as well as the inertial cavitation (IC) threshold of SPIO-albumin MBs, could be varied with different SPIO concentrations [24,25]. Here, the temperature elevations caused by sonicated SPIO-albumin MBs, regular albumin-shelled MBs, and PBS solutions w/o SPIOs in gel phantoms were recorded using a thermocouple, and the IC doses of sonicated albumin-shelled MBs and SPIO-albumin MBs were measured at varied acoustic pressure. Moreover, numerical simulations were performed based on a finite element model (FEM) to confirm the experimental results. The results provide a better understanding of how the combination of different concentrations of SPIOs affected the MBs' ability on enhancing HIFU-induced thermal effect.

2. Materials and methods

2.1. Synthesis of perfluorocarbon-filled SPIO-albumin MBs

The MBs used in the present work were synthesized by loading SPIOs into albumin-shelled perfluorocarbon MBs as mentioned elsewhere [24]. 10% bovine serum albumin and 60% sucrose were mixed with a volume ratio of 1:1 in deionized water. Then a certain amount of SPIOs (NPMag-040303, NANOEAST, Nanjing, CN) (e.g., 1.2 or 3.2 mg) were added. The mixed solution was sonicated with a horn-type ultrasonic processor (Sonics VCX750, Sonic & Materials Inc., Newtown, CT, USA) for 2 min, which worked in pulsed mode with an on/off ratio of 3:1, a working frequency of 20 kHz, and an intensity of 300 W, while a syringe pump (Legato 270, KDS, Holliston, MA, USA) was used to continuously pump in C_3F_8 gas at a speed of 7.5 mL/min. Finally, the suspension was stored at 4 °C for 4 h to make sure that the MBs reached a relatively stable level, and the upper layer of the suspension was collected for the following experiments.

The diluted SPIO-albumin and albumin-shelled MB solutions were visualized by the transmission electron microscopy (TEM, JEM-2100F, JEOL, Japan) in order to confirm that the SPIOs had been attached to the albumin-shelled MBs. The samples were applied to carbon-coated copper grids, fixed with 2.5% glutaraldehyde for 2 h at 4 °C, and then washed twice with PBS. During the TEM examination processes, the accelerating voltage of the TEM was set to be 200 kV.

2.2. Fabrication of gel phantom

The optically transparent gel phantom containing egg white was manufactured using the method proposed before [26,27]. The gel phantom contends 44.5% degassed water, 24.8% aqueous acrylamide solution with 40% concentration, 30% egg white, 0.5% of 10% ammonium persulfate and 0.2% tetramethylethylenediamine (TEMED). Before adding TEMED to solidify the phantom, the solution was degassed and then put into a columnar vessel with an inner diameter of 8 cm and a height of 5 cm with a 1 mm-diameter hydrophilic polyester tube in the middle of the height and a perpendicularly placed thermocouple (HYPO-33-1-T-G-60-SMPW-M, Omega, Omega Engineering Inc., Stamford, CT, USA).

2.3. Experimental setup

The schematic diagram of experimental setup is illustrated in Fig. 1. A home-made 1.12-MHz HIFU transducer was used as the transmitter, which was a focused spherical section transducer with a 10-cm aperture diameter and a 10-cm focal distance. The burst signals with a duty cycle of 20%, a pulse repetition frequency of 100 Hz and varied pressures were generated by an arbitrary waveform generator (33250A, Agilent, Santa Clara, CA, USA) and amplified with a 53 dB amplifier (2200L, E& I, Rochester, NY, USA). The focus of the transducer was placed at the middle of the hydrophilic polyester tube. The −3 dB focal widths in the axis and radial directions were 4.4 and 0.45 mm, respectively. The 400-times diluted MB (about 2.5–5 × 10^5 bubbles ml^{-1}) was injected continuously with a speed of 3 cm/s using a syringe pump during the sonication. A thermocouple input module (TB-9214, NI, Austin, TX, USA) was used to record the data measured by thermocouple placed in the gel with a sample frequency of 100 Hz. The whole recording time was 100 s, with sonication on for 20 s. By using a fiber optic probe hydrophone (HFO660; ONDA, Sunnyvale, CA, USA), the negative peak pressures at the focus were calibrated to be 1.52, 2.33, 3.43, 4.53, and 5.64 MPa, respectively. Two SPIO-albumin MB solutions with different SPIO concentrations, albumin-shelled MB solution, phosphate buffer saline (PBS) containing SPIOs and pure PBS solution were tested in the present work. Each experiment was repeated three times after the water in the tank cooled down to the room temperature. A 5-MHz transducer (V326-SU, Panametrics, Waltham, MA) was placed 45° to the focal region of the 1.12-MHz transducer to measure the IC dose generated by the sonicated samples and the detected signals were digitalized by and displayed on a digital oscilloscope (54830B, Agilent, Santa Clara, CA) with a sampling frequency of 25 MHz; each signal contained 32,768 data points. For each kind of MBs, 50 signals were measured during 20-s sonication. Finally, the IC doses generated by the albumin-shelled MBs and SPIO-albumin MBs were quantified by using the method that had been detailed described elsewhere [28].

2.4. Theoretical model

The acoustic field of the transducer could be described with the two-dimensional (2D) Helmholtz equation [29]

$$\frac{1}{\rho_0}\frac{\partial^2 p}{\partial z \partial \tau} = \frac{1}{\rho_0}\frac{c_0}{2}\Delta_{\perp} p \tag{1}$$

where p is the acoustic pressure, z is the coordinate along the beam axis, $\tau = t - z/c_0$ is the time delay with t being time, c_0 and ρ_0 are the sound speed and density of the medium, respectively. $\Delta_{\perp} = \partial^2/\partial x^2 + \partial^2/\partial y^2$ is the transverse Laplacian operator in Cartesian coordinates. In the simulation, COMSOL® Multiphysics 5.2a (COMSOL, Burlington, MA, USA) was used to explore the characteristics of acoustic fields. To save the memory of calculating, "Pressure Acoustic, Frequency Domain" physics in COMSOL® was utilized to simulate 2D acoustic fields, which takes the form

$$\nabla\left(-\frac{1}{\rho_0}(\nabla p)\right) = \frac{k^2 p}{\rho_0} \tag{2}$$

where $k = c_0/\omega - i\alpha$ is the wave number, α is the acoustic absorption coefficient. The method used in the present work was similar to that was described in detail elsewhere [30]. In brief, the acoustic pressure at the focal region was measured first in the water, then a 2-D model was used to compute the pressure at the surface of the transducer. Finally, the surface pressure was adopted as the boundary condition to further simulate the pressure field in the phantom.

The temperature field generated by sonication is determined with the Pennes bioheat transfer equation [31]. It contains two domains and can be expressed as

$$\frac{\partial T}{\partial t} = \frac{K_g}{\rho_g C_g}\nabla^2 T + \frac{Q_d}{\rho_g C_g}\,(\text{gel domain}), \tag{3}$$

$$\frac{\partial T}{\partial t} = \frac{K_v}{\rho_v C_v}\nabla^2 T - \rho_v C_v(\mathbf{u}\cdot\nabla T) + \frac{Q_d}{\rho_v C_g}\,(\text{vessel domain}), \tag{4}$$

where $Q_d = 2\alpha I = 2\alpha|\mathrm{Re}(1/2\ p\mathbf{v})|$ is the dissipated power density, I is the acoustic intensity magnitude, $\mathbf{v}$ is the acoustic particle velocity vector, T is the temperature, ρ, C and K are the density, specific heat and thermal conductivity of the domain (gel or vessel) which is referred by