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# Microwave-induced thermoacoustic computed tomography with a clinical contrast agent of $\text{NMG}_2[\text{Gd}(\text{DTPA})]$

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$\text{NMG}_2[\text{Gd}(\text{DTPA})]$ , a clinical contrast agent, was investigated for microwave-induced thermoacoustic computed tomography (CT). Due to ionic conduction and magnetic dipole rotation in the presence of microwave field, microwave energy absorbed by  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  would be transformed to thermoacoustic signals based on the thermoelastic effect. The experimental results demonstrated that  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at a concentration of 10 mM provided effective enhancement compared with water. The enhancement of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  for thermoacoustic CT was further demonstrated in *in vivo* tumor-bearing mouse. The theory and experimental results indicate that the clinically available  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  will promote the medical applications of thermoacoustic CT. © 2012 American Institute of Physics. [doi:10.1063/1.3678022]

Microwave-induced thermoacoustic (TA) computed tomography is a hybrid of microwave imaging and ultrasound imaging, which integrates high microwave contrast and good ultrasound resolution in single imaging modality. Microwave-induced thermoacoustic effect is based on the thermoelastic mechanism.<sup>1</sup> When a sample is illuminated by the pulsed microwave, the absorber expands due to thermoelastic expansion, and then the TA wave is generated under the conditions of thermal and stress confinement. The TA wave can be captured by an ultrasonic transducer and processed for TA image. Within the vaporization threshold of the employed microwave energy, the TA signal amplitude is in linear relationship with the microwave energy absorption.<sup>2</sup> Therefore, thermoacoustic computed tomography (CT) can reflect the distribution of microwave absorption inside the biological tissues.

Thermoacoustic CT offers higher spatial resolution than microwave imaging and receives much deeper imaging than most optical imaging techniques. The recent surge of interest has expanded the depth of thermoacoustic CT techniques to biomedical imaging, such as breast cancer imaging, foreign body detection, and targeted tumor detection.<sup>3,4</sup> Thermoacoustic CT typically utilizes the endogenous agent (water) in tissue as image contrast. Exogenous contrast agents will enhance the contrast in the deeper region. Some contrast agents for thermoacoustic CT have been suggested previously, such as single-walled nanotubes, microbubbles, and magnetic nanoparticles.<sup>5-7</sup> But so far, none of them is approved for clinical application, and their clinical applicability still needs to be researched. Paramagnetic gadolinium chelate (Magnevist<sup>®</sup>,  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ :  $\text{NMG}$  = N-methylglucammonium;  $\text{Gd-DTPA}$  = the gadolinium complex of diethylenetriamine pentaacetic acid) is used for MRI.<sup>8</sup>  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  is a paramagnetic ionic contrast agent with seven unpaired electrons in the 4f orbital of the  $\text{Gd}^{3+}$ . The charged ions and unpaired electrons can interact with microwave field and transform the absorbed microwave energy into heat.

In this paper, we investigate the feasibility of using a clinical contrast agent of paramagnetic gadolinium chelate ( $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ ) for microwave-induced thermoacoustic CT. First, we analyzed the reasons why  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  could enhance thermoacoustic signal amplitude. Second, The enhanced effect of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  for thermoacoustic CT was verified *in vitro* and *in vivo* experiments. Experimental results demonstrated that compared with water,  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at a concentration of 10 mM could provide effective enhancement (11.3%). The  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  can increase the ionic conductivity and microwave absorption coefficient of tumors. Therefore, the boundary between tumor and normal tissue is more obvious in thermoacoustic imaging.

The condition of stress confinement has to be met in TA wave generation. When the microwave energy is deposited in the sample within a short time, the thermal diffusion effect is usually negligible. Under the condition, the excited thermoacoustic pressure is determined by the local microwave energy absorption. The thermoacoustic pressure can be written as follows:<sup>9-13</sup>

$$P(z) = (\beta C_0^2 / C_p) \mu_a H = \Gamma \mu_a H(z) = \Gamma \mu_a H_0 e^{(-\mu_a z)}, \quad (1)$$

where  $P(z)$  represents the thermoacoustic pressure at the vertical distance from the radiator. The expression of  $\beta C_0^2 / C_p$  is the Grüneisen parameter ( $\Gamma$ ) that represents the transformation of thermal to stress.  $z$  is the vertical distance from the radiator, and  $e^{(-\mu_a z)}$  represents the attenuation of the microwave field strength as a function of distance from the radiator. According to Eq. (4), at the same vertical distance from the radiator, as the microwave field absorption coefficient  $\mu_a$  increase, the thermoacoustic pressure  $P(z)$  will increase. Furthermore, the  $\mu_a$  is determined by the following equation:<sup>3</sup>

$$\mu_a = \omega \sqrt{\frac{\mu \varepsilon}{2} \left[ \sqrt{1 + \left( \frac{\sigma}{\omega \varepsilon} \right)^2} - 1 \right]}, \quad (2)$$

where  $\omega$  is the angular frequency,  $\mu$  is the permeability,  $\varepsilon$  is the permittivity, and  $\sigma$  is the conductivity. The purpose of

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this paper is to demonstrate that  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  can be used as a contrast agent for thermoacoustic CT. Therefore, we have to analyze the microwave absorption properties of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ . Schematic of TA signal generation process is shown in Fig. 1. First, when  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  is dissolved in water, there are two types of charged ion in the solution:  $\text{NMG}^+$  and  $[\text{Gd}(\text{DTPA})]^{2-}$ . These charged ions would migrate in the presence of a microwave field, which lead to a conductivity increase of the solution.<sup>14</sup> According to Eq. (2), as the conductivity increased, microwave field absorption coefficient increased accordingly. Water is a well-known source of microwave absorber in the human body. The molar conductivity of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  is  $117 \text{ Smcm}^2/\text{mol}$ , while de-ionized water is  $10^{-5} \text{ Smcm}^2/\text{mol}$ .<sup>17</sup> According to Eqs. (1) and (2), the microwave field energy absorbed by the  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  solution would improve as the conductivity increased, which resulted in the increase of TA amplitude over water. Second, the microwave field absorption properties of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  also correlated with the seven unpaired electrons in the 4f orbital of the  $\text{Gd}^{3+}$ . Unpaired electronic spins behave as magnetic dipoles with a moment of one Bohr magneton. Magnetic dipoles are expected to interact with the oscillating magnetic component of microwave radiation and be able to absorb microwave energy when the magnetic vector are rotated with the oscillating magnetic and strayed from the steady state.<sup>15,16</sup> However, there were no unpaired electrons in the water molecule. We can conclude that  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  solution possesses stronger microwave absorption than water, which results in the enhancement of TA signal. Besides,  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  is a clinical contrast agent, so the research will be a great advance in thermoacoustic CT clinical application.

In order to show that  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  can be used as a thermoacoustic CT contrast agent, TA signal of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at clinical injection concentration (0.5 M) was measured and compared with water, blood, muscle, and fat by our 6 GHz thermoacoustic CT system. The TA signals generated by  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  solution, water, blood, muscle, and fat are displayed in Fig. 2(a). The error bars represent

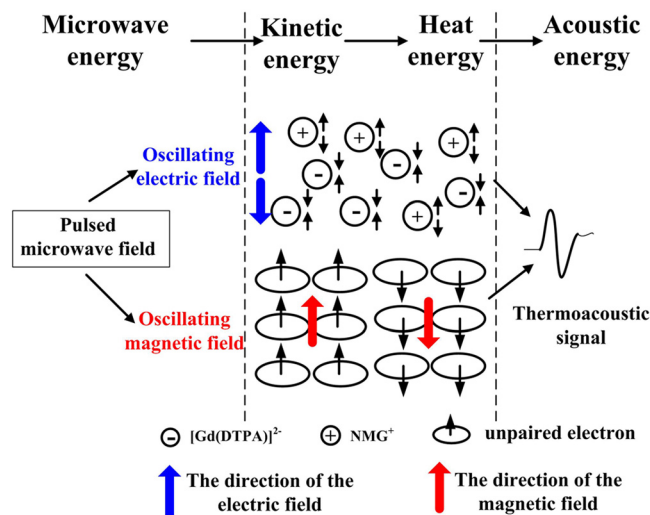


FIG. 1. (Color online) Schematic of TA signal generation theory of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  agent.

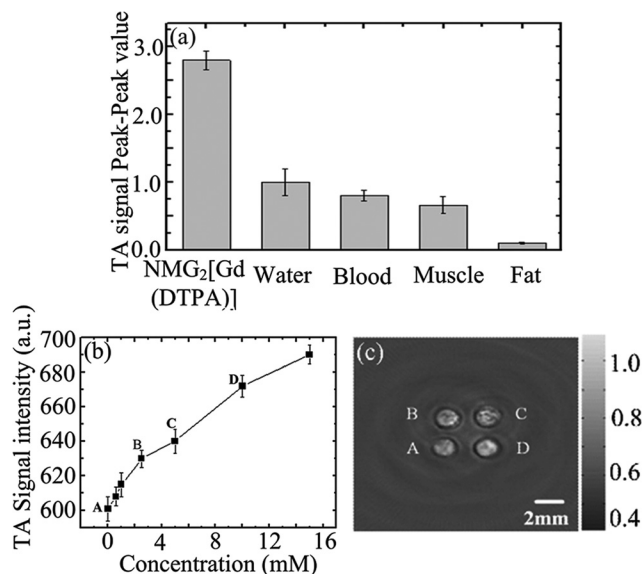


FIG. 2. (a) TA signal generated by  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  solution at clinical injection concentration (0.5 M) and different biological tissues. (b) TA signals of the  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at different concentrations. The error bars represent standard deviation obtained from 10 measurements. (c) Thermoacoustic CT of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at four different concentrations in plastic tubes with a diameter of 1.8 mm which were embedded in paraffin. A: water, B: 2.5 mM  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ , C: 5 mM  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ , D: 10 mM  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ .

standard deviation obtained from 10 measurements. The TA signal produced by  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  solution was much stronger than that produced by water. As expected, the result is consistent with the above theoretical analysis. Due to blood, muscle, and fat containing water, TA signals can be generated from those tissues. The difference of water content in the tissues leads to different microwave absorption, thereby, generating different TA signal amplitude on different biological components. Another experiment was performed to determine the concentration of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  for effective enhancement in thermoacoustic CT. TA signal intensities of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at different concentrations were measured as shown in Fig. 2(b). The results clearly exhibit the dependence of TA amplitude on the concentration of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ . Moreover, this dependency is also valid for samples with different microwave absorption coefficients. With the increase of concentration, TA signal of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  increase. Four identical plastic tubes with a diameter of 1.8 mm that filled with different concentrations of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  solution were embedded in paraffin and were imaged by thermoacoustic CT. The tubes marked "A" was filled with water, and the tube marked "B," "C," and "D" were filled with  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at a concentration of 2.5 mM, 5 mM, 10 mM, respectively. The thermoacoustic CT in Fig. 2(c) was obtained by circular scanning at 200 scanning positions. A high-contrast thermoacoustic CT can be reconstructed with high signal-noise-ratio (SNR) TA signals. As shown in Fig. 2(c), when the concentration of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  increased, the SNR of the absorber imaging increased accordingly, which clearly demonstrated the advantage of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  enhancement. Map of tube "D" containing  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  had a much higher SNR than the tube "A" containing only water for the exogenous contrast agent that had higher microwave absorption.

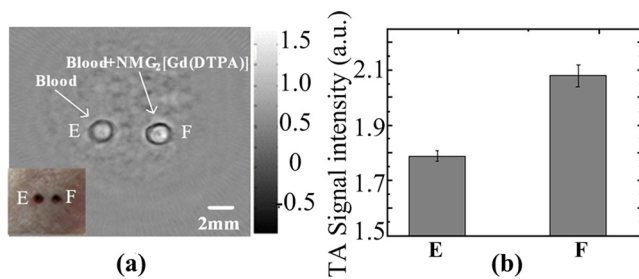


FIG. 3. (Color online) (a) Thermoacoustic CT of human blood mixed with and without  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  in plastic tubes which were embedded in pork muscle tissue. Actual phantom was shown in the inset. E: blood, F: 10 mM  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  mixed with blood. (b) The quantitative results of (a).

According to the result, the TA signal SNR of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  at a concentration of 10 mM can be increased roughly 11.3% compared with that of water, which was an effective enhancement. The result indicated that  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  has a potential to improve tissue contrast in thermoacoustic CT.

To further prove,  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  can enhance TA signal of tissue. Two plastic tubes: the tube marked “E” was filled with blood and another one marked “F” was filled with blood which, mixed with  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  (the concentration was about 10 mM), were embedded in pork muscle tissue for thermoacoustic CT. In the thermoacoustic CT experiment, the reconstructed image in Fig. 3(a) agreed well with the actual phantom as shown in the inset. The thermoacoustic CT of tube “F” containing  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  and blood had a higher SNR than that of the tube “E” containing blood due to the higher microwave absorption of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ . The quantitative results of Fig. 3(a) are shown in Fig. 3(b). When  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  was at a concentration of 10 mM in the blood, the TA SNR of “F” increased roughly to 16.2% compared with that of the blood sample “E.” This study shows that the  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  would be a clinical contrast agent for thermoacoustic CT.

In order to examine the capability of thermoacoustic CT to detect tumor with  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  as the contrast agent, *in vivo* tumor experiments were performed 2 weeks after tumor inoculation on the mice back. Figs. 4(a) and 4(b) image were taken before and after *in situ* injection with  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ . In the reconstructed thermoacoustic images, the tumor model of outer bright ring in the thermoacoustic image represents the boundary between the tumor and the normal tissue corresponding to the cancer invasion front with rapid cell proliferation and robust angiogenesis in the tumor. A small increase in ionic conductivity can significantly increase the microwave absorption at the margins of the tumor. After *in situ* injection of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ , the ionic conductivity of tumor can be increased and results in increase of its microwave absorption coefficient, so the boundary between tumor and normal tissue becomes more obvious in thermoacoustic imaging (Fig. 4(b)). These results suggest that by using  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  as contrast agents,

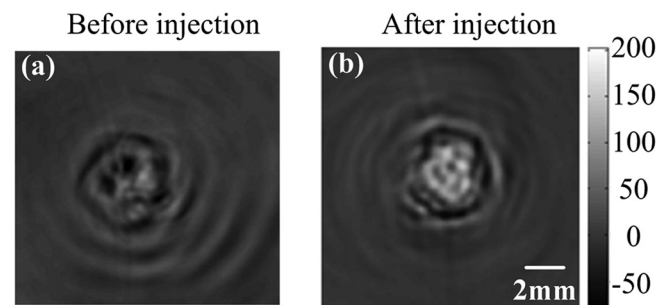


FIG. 4. Thermoacoustic CT of tumor bearing mouse before injection of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  (a) and after *in situ* injection of  $\text{NMG}_2[\text{Gd}(\text{DTPA})]$  (b).

thermoacoustic CT is generally suitable to delineate tumor edge.

In summary, the ability of a clinically used contrast agent for thermoacoustic CT was testified and demonstrated. The theory and experiment results turned out that paramagnetic gadolinium chelate ( $\text{NMG}_2[\text{Gd}(\text{DTPA})]$ ) can be used as a contrast agent for thermoacoustic CT, which would be suitable for delineation of tumor edges. The research can lead to a great advance in the clinical application of thermoacoustic CT.

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