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● *Original Contribution*

A TISSUE MIMICKING POLYACRYLAMIDE HYDROGEL PHANTOM FOR VISUALIZING THERMAL LESIONS GENERATED BY HIGH INTENSITY FOCUSED ULTRASOUND

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Abstract—An optically transparent tissue-mimicking (TM) phantom whose acoustic properties are close to those of tissue was constructed for visualizing therapeutic effects by high intensity focused ultrasound (HIFU). The TM phantom was designed to improve a widely used standard bovine serum albumin (BSA) polyacrylamide hydrogel (PAG), which attenuated ultrasound far less than tissue and, unlike tissue, did not scatter ultrasound. A modified recipe has been proposed in the study by adding scattering glass beads with diameters of 40–80 μm (0.002% w/v) and by raising the concentration of acrylamide (30% v/v). The TM BSA-PAG constructed has an acoustic impedance of 1.67 MRayls, a speed of sound of 1576 m/s, an attenuation coefficient of 0.52 dB/cm at 1 MHz, a back-scattering coefficient of 0.242×10^{-3} 1/sr/cm at 1 MHz and a nonlinear parameter (B/A) of 5.7. These parameters are close to those of liver. The thermal and optical properties are almost the same as the standard BSA-PAG. The characteristic features of the thermal lesions by HIFU were observed to be more accurately visualized in the TM BSA-PAG than in the standard BSA-PAG. In conclusion, the proposed TM BSA-PAG acoustically mimics tissue better than the standard BSA-PAG and is expected to be preferentially used for assuring if a clinical HIFU device produces the thermal lesion as planned. (E-mail: mjchoi@jejunu.ac.kr) **© 2013 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Tissue mimicking (TM), Phantom, High intensity focused ultrasound (HIFU), Ultrasound, Polyacrylamide hydrogel (PAG), Bovine serum albumin (BSA), Visualization, Thermal lesion.**

INTRODUCTION

The minimally invasive nature of high-intensity focused ultrasound (HIFU) surgery offers an advantage over other therapeutic means in tumor treatment (Beerlange et al. 1999; ter Haar et al. 2001; Vaezy et al. 2001; Wu et al. 2001). To ensure patient safety and to maintain clinical efficacy in HIFU surgery, routine quality assurance (*i.e.*, testing whether a HIFU device produces the thermal lesion as designed) is of importance. A tissue-mimicking (TM) phantom, which, in particular, acoustically mimics a target tissue, is critical in the quality assurance.

An optically transparent polyacrylamide hydrogel (PAG) with a temperature-sensitive indicator such as bovine serum albumin (BSA) (Khokhlova et al. 2006) or egg white (Takegami et al. 2004) has been used extensively for years for visualizing HIFU-induced thermal lesions. Lafon et al. (2005) performed studies on such a PAG, characterizing its acoustic and optical properties. The Lafon recipe is widely used as a standard for HIFU studies. The key acoustic properties of the standard BSA-PAG, however, are not particularly suited for use in tissue mimicking. For example, it has an attenuation coefficient approximately 60% less than that of tissue and, unlike tissue, does not scatter ultrasound (Choi et al. 2012a; Lafon et al. 2005). A gelatin-based phantom was reported to possess mechanical, acoustic, and optical properties similar to those of the human bladder (Ejofodomi et al. 2010). The phantom attenuates and scatters ultrasound like human tissue, but it is not optically transparent because it was designed to scatter light like tissue as well.

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The thermal lesion formed in a medium by HIFU is obviously dependent on the acoustic and thermal properties of the medium (Bush et al. 1993; Gertner et al. 1997). It seems likely that the differences between BSA-PAG and real tissue account for the small lesion volumes reported by Lafon et al. (2005) compared with those in tissue for the same HIFU dose. The lack of scattering in BSA-PAG also makes it difficult to ultrasonically image HIFU lesions unless cavitation or boiling bubbles are generated.

In the present study, we attempted to modify the recipe of the BSA-PAG described by Lafon et al. (2005), named hereafter as the *standard BSA-PAG*, aimed at making a BSA-PAG that more closely mimics the acoustic scattering and attenuation of biological tissues. The modification included the insertion of glass beads as ultrasonic scatterers and involved increasing the concentration of acrylamide to enhance ultrasonic absorption. The acoustic, optical, and thermal properties of the modified TM BSA-PAG were measured, and HIFU lesion formation was compared with that in the standard BSA-PAG and tissue.

MATERIALS AND METHODS

TM PAG preparation

The recipe by Lafon et al. (2005) was modified to construct the TM BSA-PAG by inserting glass beads as ultrasonic scatterers and by increasing the concentration of acrylamide to raise ultrasonic absorption. The glass beads have a diameter of 40–80 μm and a density of 2.5 g/cm^3. The concentration of the glass beads was determined empirically to be 0.002% w/v from the measurement of the ultrasonic backscatter coefficients of the glass bead-water solution while its concentration varied. The acrylamide concentration was also experimentally chosen to be 30% v/v so that the attenuation coefficient was similar to liver tissue. Note that the relative amount of water was reduced to increase the acrylamide concentration. Further details of these empirical selections are given in the Discussion. The modified recipe for the TM PAG (for a volume of 50 mL) is presented in Table 1 in contrast to that of Lafon et al. (2005), which represents the standard BSA-PAG.

The TM PAG was prepared by first mixing the 7% (w/v) BSA (A7906; Sigma-Aldrich, St. Louis, MO, USA) in degassed distilled water. The mixture was gently stirred until the BSA was completely dissolved in the water. Next, the solution was placed in a vacuum chamber (OV-01/02; Jeio Tech, Seoul, Republic of Korea) and was held in a vacuum of 720 mm Hg strength for 30 minutes. The 30% (v/v) aqueous solution of 40% (w/v) acrylamide with an acrylamide to bis monomer cross-link ratio of 19:1 (A9926; Sigma-Aldrich) was added to the mixture,

Table 1. Composition of 50 mL of the proposed TM BSA-PAG, which modifies the recipe of Lafon et al. (2005) by inserting glass beads and by increasing the acrylamide concentration

Components	Quantity	Proportion (%)
Distilled water	29.64 mL	59.28 (v/v)
Bovine serum albumin	3.5 g	7.00 (w/v)
1 M TRIS buffer (pH 8)	5 mL	10.00 (v/v)
40% (w/v) Acrylamide: bis monomer	15 mL	30.00 (v/v)
Glass bead (40–80 μm)	0.01×10^{-1} g	0.2×10^{-2} (w/v)
10% (w/v) APS	0.42 mL	0.84 (v/v)
TEMED	0.025 mL	0.05 (v/v)

APS = ammonium persulfate; BSA = bovine serum albumin; PAG = polyacrylamide hydrogel; TEMED = tetramethylethylenediamine; TM = tissue-mimicking.

followed by 10% (v/v) of 1 mol/L of TRIS buffer at pH 8 (Trizma hydrochloride and Trizma base; Sigma-Aldrich) and 0.84% (v/v) of 10% (w/v) ammonium persulfate (APS) solution (A7460; Sigma-Aldrich) to initiate polymerization. The TRIS buffer controls the pH value of the entire solution, which influences the thermal denaturation of BSA (Donald et al. 2004). Acrylamide monomer is a neurotoxic substance and therefore must be handled in a fume hood with appropriate safety gloves, goggles and laboratory coat.

The entire solution was mixed gently until the solution was homogenized. Next, it was placed in the vacuum chamber and held under a vacuum of 720 mm Hg strength for more than 1 h for additional degassing. In the next step, 0.002% (w/v) of glass beads was added to the mixed solution, ensuring that they were distributed uniformly in the mixture. Finally, a small amount (0.05% v/v) of the polymerization agent of N, N, N′, N′-tetramethylethylenediamine (T2694; Sigma-Aldrich) was added to the mixture to accelerate the rate of the formation of free radicals from persulfate, and these in turn catalyzed the solution for polymerization. The final solution was immediately poured into a rectangular hexahedral acrylic container. An exothermic reaction during polymerization was expected because of the high percentage of acrylamide, so the surrounding temperature had to be maintained at less than 10°C until polymerization was complete. This prevented the temperature in the mixture during polymerization from rising higher than the threshold level (~50°C) for denaturation of the protein. The polymerized gel was stored in an air-tight container at a temperature of 4°C in a refrigerator before it was used for experiments.

Measurements of TM BSA-PAG properties

Acoustic properties. The acoustic parameters measured on the TM BSA-PAG included the speed of sound, the frequency dependent attenuation, the