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Reusable tissue-mimicking hydrogel phantoms for focused ultrasound ablation

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ABSTRACT

The ability of N-isopropylacrylamide (NIPAM)-based hydrogel phantoms to mimic tissues with different acoustic and thermal properties under high-intensity focused ultrasound (HIFU) ablation was investigated. These phantoms were designed to model the formation of thermal lesions in tissues above the threshold temperature of protein denaturation. By adjusting the concentration of acrylic acid (AAc) in the NIPAM-based hydrogel phantoms, the cloud point (i.e., lower critical solution temperature) of the phantoms could be tailored to produce HIFU thermal lesions similar to those formed in different swine tissues in terms of size and shape. Additionally, energy thresholds for inducing transient or permanent bubbles in the phantoms during HIFU ablation were also identified to shed light on the onset of cavitation or material damage. The NIPAM-based hydrogel phantoms developed in this study possess major advantages such as transparent, reusable and tailorable properties, and are practical tools for characterizing an ablative device (or treatment) to determine its efficacy and safety.

1. Introduction

In recent years, less-invasive ablative modalities using thermal energy, such as laser, focused ultrasound, microwave, and radiofrequency ablations, have received considerable attention, especially for localized tumor ablation [1–6]. To expand potential applications and avoid in vivo experiments or human experimentations, the design and processing of transparent tissue-mimicking phantoms capable of demonstrating the evolution and extent of thermal lesion formation in real time are extremely helpful for all ablative devices during preclinical development.

Several temperature-sensitive tissue-mimicking phantoms have been reported as model materials for ablative therapy. For example, polyvinyl alcohol (PVA) or agar-based phantoms were used to visualize the effect of bubble-enhanced heating by focused, MHz-frequency ultrasound [7]. However, thermal lesions could not be well visualized in such phantoms. Transparent polyacrylamide (PAA) gels containing bovine serum albumin (BSA) were then proposed since BSA would turn white and optically opaque or reduce the T2 signal on magnetic resonance imaging upon reaching the threshold temperature of protein denaturation [8–10]. Takegami et al. demonstrated a low-cost version by replacing BSA with egg white for the study of focused ultrasound ablation [11]. Although easily fabricated, the major disadvantages associated with egg white or albumin-based tissue-mimicking phantoms are the irreversible protein denaturation and permanent color change above the threshold temperature, making them impossible to be reused.

To solve the above-mentioned disadvantages, new temperature indicators were adopted to replace BSA for the construction of tissue-mimicking phantoms. For example, a nonionic surface-active agent (NiSAA) which exhibited hydrophobic segregation at temperatures above the so called "cloud point" temperature was proposed [12]. The cloud point, also known as the lower critical solution temperature (LCST), represents the temperature when macromolecules transform from a hydrophilic structure (below the cloud point) to a hydrophobic structure (above the cloud point) [13]. For example, polyacrylamide hydrogels containing NiSAA

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were shown to become opaque when heating above the cloud point, but gradually return to transparent upon cooling [12]. The cloud point of the polyacrylamide hydrogels could be altered by the choice of NiSAA type and further finely adjusted with the addition of methanol or butanol, or by changing the pH value [12].

Similar temperature-sensitive properties to NiSAA can also be found in N-isopropylacrylamide (NIPAM) and polyNIPAM copolymers which possess cloud points near physiological relevant temperatures [13,14]. Our previous study has demonstrated that heating a transparent NIPAM-based hydrogel phantom above the cloud point would lead to the segregation of NIPAM, resulting in the increase of opaqueness at the heating area [16]; moreover, the color (opacity) change is reversible upon cooling, making the phantom a reusable modeling tool. Other major advantages of the NIPAM-based tissue-mimicking phantom are the similarity of its acoustic properties to those of human tissue, and that its threshold temperature (i.e., LCST) could be easily manipulated by the addition of acrylic acid (AAc) [14–16].

This study reports the endeavor to utilize AAc-controlled NIPAM-based hydrogel phantoms to mimic the actual shape and size of thermal lesions formed by high-intensity focused ultrasound (HIFU) ablation in different target tissues. Two types of swine tissues, pork tenderloin and brain, with distinct acoustic properties were modeled by the NIPAM-based phantoms for their behaviors under HIFU. The critical energy which may induce transient or permanent bubbles in the phantoms was also characterized to shed light on the cavitation onset or material damage threshold. Due to their reusability and high modeling flexibility, the AAc-controlled NIPAM-based hydrogel phantoms would be useful for the rapid characterization and calibration of an ablative device/treatment for different target tissues, and could be used to determine the efficacy and safety of the device/treatment before performing actual ablations.

2. Materials and methods

2.1. Preparation of NIPAM-based hydrogel phantoms

The NIPAM-based reusable hydrogel phantoms were formed by crosslinking copolymerization of NIPAM and N,N'-methylenebisacrylamide (MBAm) with the addition of AAc to adjust the cloud point so that it fell in the temperature range of biological significance [16]. The NIPAM-based phantom with cloud point temperature at 52 °C is denoted as "NIPAM-52" phantom in this study. 52 °C was chosen since it represents the threshold temperature above which an irreversible tissue damage may occur. The constituents of the NIPAM-52 phantom and their amounts are listed in Table 1. The fabrication process consisted of the following steps: 0.44 ml or volume ratio 0.274% of AAc (99.5%, Acros Organics, USA) was first dissolved in 150 ml degassed, distilled water before adding 9 g of NIPAM (Acros Organics, USA) to the aqueous solution. The solution was gently stirred at room temperature until complete dissolution of NIPAM. 0.375 g of MBAm (97%, Alfa Aesar, UK) and 0.195 g of ammonium persulfate (APS; Sigma Chemicals, USA), which acted as the initiator for crosslinking, were then added consecutively into the aqueous solution. The mixture was gently stirred at room temperature until homogenized. Finally, 0.4 ml of polymerization agent N,N,N',N'-tetramethylethylenediamine (TEMED; 99%, Sigma Chemicals, USA) was added to the mixture. The final aqueous mixture was immediately poured into molding containers and allowed to polymerize completely at room temperature to form hydrogel phantoms as shown in Fig. 1a. The hydrogel phantoms prepared were either tested in the ablation experiments within 24 h after complete polymerization, or stored in an airtight container to avoid dehydration (if left in air) or swelling (if placed in water) for later experimental usage. The NIPAM-based hydrogel phantoms were optically transparent, gelatin-like materials (see Fig. 1a).

In order to match the shape and size of coagulation lesions in different swine tissues, NIPAM-based phantoms containing different amounts of AAc, ranging from 0.25 to 0.85 ml, were fabricated. The cloud point temperature of the NIPAM-based hydrogel phantom changes with the concentration of AAc. At a fixed ablation power level, a lower AAc concentration would result in a lower cloud point, and thus a larger ablation lesion.

Table 1
Constituents of NIPAM-52 and egg-white-based hydrogel phantoms.

	NIPAM-52	Egg white
Degassed water	150 ml	10.5 ml
AAc	0.44 ml	–
NIPAM	9 g	–
MBAm	0.375 g	–
APS	0.195 g	0.05 g
TEMED	0.4 ml	0.4 ml
Egg white	–	60 ml
Acrylamide	–	24.8 ml
Anhydrous glycerol	–	4.5 ml

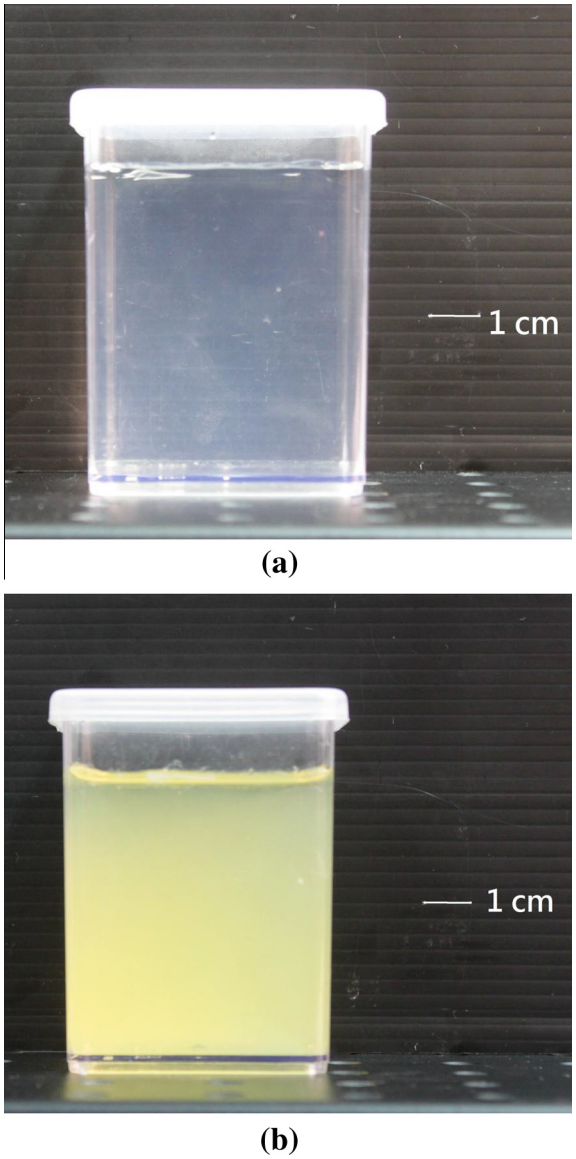

Fig. 1. Optical images of (a) NIPAM-52 and (b) egg-white-based hydrogel phantoms.