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Acrylic acid controlled reusable temperature-sensitive hydrogel phantoms for thermal ablation therapy

Jay Shieh [a,1], Shing-Ru Chen [b,c,1], Gin-Shin Chen [b], Chia-Wen Lo [c], Chuin-Shan Chen [d], Ben-Ting Chen [e], Ming-Kuan Sun [c], Chang-Wei Huang [e,**], Wen-Shiang Chen [b,c,*]

[a] Department of Materials Science and Engineering, National Taiwan University, Taipei, Taiwan
[b] Division of Medical Engineering Research, National Health Research Institutes, Miaoli, Taiwan
[c] Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital & College of Medicine, Taipei, Taiwan
[d] Department of Civil Engineering, National Taiwan University, Taipei, Taiwan
[e] Department of Civil Engineering, Chung Yuan Christian University, Chung Li 32023, Taiwan

HIGHLIGHTS

- A method to fabricate a transparent reusable tissue-mimicking phantom was proposed.
- The phantom changes color at a preselected threshold temperature.
- The threshold temperature can be adjusted by the concentration of acrylic acid.
- The phantom was designed for the real-time visualization of thermal lesions.

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ABSTRACT

Polymerization of *N*-isopropylacrylamide (NIPAM) with acrylic acid (AAc) has been adopted to fabricate reusable tissue-mimicking hydrogel phantoms designed for the real-time visualization and examination of thermal lesion formation in ablation and hyperthermia therapies. It is shown that the cloud point temperature of the NIPAM-based hydrogel phantoms can be adjusted by the concentration of AAc to represent the threshold temperature of pain (42 °C) or tissue damage (52 °C). The mechanical, thermal and acoustic properties of the developed phantoms are similar to those of human soft tissues. The ability of the phantoms to provide visualization of thermal lesions produced by either microwave or high-intensity focused ultrasound (HIFU) ablation was examined. Evolution of the optical transparency of the phantoms with temperature was found to be a stable hysteretic behavior and reproducible in consecutive heating–cooling cycles, demonstrating the reusability of the phantoms. By processing the optical images of the phantoms at different stages of the heating process, a thermal lesion can be considered formed (i.e., threshold temperature reached) when the grayscale value reaches the half-saturation point. The image processing method proposed for the NIPAM-based hydrogel phantoms is shown to be independent on the type of heating device used.

1. Introduction

Less-invasive ablative modalities using thermal energy, such as laser ablation, focused ultrasound, microwave ablation, and radiofrequency ablation etc., have received considerable attention in recent years, especially for localized tumor ablation [1–6]. To extend potential applications and avoid in-vivo experiments or human experimentations, a transparent tissue-mimicking phantom which is able to demonstrate the process and extent of thermal lesion formation in real time is critical important for

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* Corresponding author. Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei, Taiwan. Tel.: +886 2 23123456x67087; fax: +886 2 23832834.

** Corresponding author. Department of Civil Engineering, Chung Yuan Christian University, Chung Li , Taiwan. Tel.: +886 3 2654206; fax: +886 3 2654299.

E-mail addresses: cwhuang@cycu.edu.tw (C.-W. Huang), wenshiang@gmail.com (W.-S. Chen).

[1] Equal contribution.

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all ablative devices during preclinical development and surgical planning.

Several temperature-sensitive tissue-mimicking phantoms have been reported as models for ablative therapy. For example, polyvinyl alcohol or agar-based phantoms were used to visualize the effect of bubble-enhanced heating [7] by focused, MHz-frequency ultrasound. 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 cause a large reduction in the T2 signal on magnetic resonance imaging upon reaching the threshold temperature of protein denaturation [8,9]. Takegami et al. demonstrated a low-cost version by replacing BSA with egg white [10] for the study of focused ultrasound ablation. 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. Moreover, precise identification and adjustment of the threshold temperature of the phantoms are difficult to achieve.

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 [11]. 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) [12]. For example, polyacrylamide hydrogels containing NiSAA were shown to become opaque when heating above the cloud point, but gradually return to transparent upon cooling [11]. 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 [11].

Similar temperature-sensitive properties to NiSAA can also be found in *N*-isopropylacrylamide (NIPAM) and PolyNIPAM copolymers which exhibit cloud points near physiological relevant temperatures [12,13]. Existing studies have shown that heating an aqueous NIPAM solution past the cloud point would lead to the segregation of NIPAM, resulting in the increase of opaqueness of the solution [12,14]. Moreover, the acoustic properties of NIPAM or polyNIPAM copolymer gels are similar to those of human tissue [15], and their temperature and optical properties, including LCST and transparency, could be easily manipulated by the addition of acrylic acid (AAc) [13,16].

This study reports a method based on polymerization of NIPAM in the presence of AAc for the fabrication of reusable tissue-mimicking hydrogel phantoms, which are designed for the real-time visualization and examination of thermal lesion formation in microwave and high-intensity focused ultrasound (HIFU) ablation therapies. In order to understand the similarity (or dissimilarity) between the phantoms developed and human tissue, key mechanical, thermal, acoustic and optical properties of the phantoms must also be characterized. Two types of NIPAM-based reusable hydrogel phantoms with cloud point temperatures at 42 and 52 °C were prepared for the microwave and HIFU ablation experiments; they are denoted as “NIPAM-42” and “NIPAM-52” phantoms, respectively, in this study. The cloud point was adjusted by the concentration of AAc and the two chosen threshold temperatures, 42 and 52 °C, represent the thresholds of pain and tissue damage [17], respectively. Pain is typically experienced at temperatures above 42 °C, while irreversible tissue damage may occur above 52 °C. The NIPAM-based phantom systems demonstrated in this study are therefore useful for the rapid characterization and calibration of an ablative device/treatment to determine its efficacy and safety before animal or clinical studies.

2. Materials and methods

2.1. Preparation of 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. The constituents of the phantoms and their amounts are listed in Table 1. The fabrication process consisted of the following steps: AAc (purity 99.5%) with an amount of either 0.19 or 0.44 ml was dissolved in 150 ml degassed, distilled water first – these two specific amounts of AAc gave rise to the cloud points of 42 and 52 °C, respectively. Next, 9 g of NIPAM was added to the aqueous solution, which was gently stirred at room temperature until complete dissolution of NIPAM. 0.375 g of MBAm (purity 97%) and 0.195 g of ammonium persulfate (APS), 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*′-tetramethyl-ethylene (TEMED; purity 99%) 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. 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.

2.2. Measurement of density and elastic modulus

For the measurements of mechanical properties, the hydrogel phantoms were cut into cuboidal specimens measuring 5 × 5 × 5 cm^3. The apparent densities of the specimens were determined by the standard Archimedes’ immersion technique, i.e., dividing the weight of the specimen (measured by an electronic balance) by its volume (equaled to the volume of water displaced) when the specimen was suspended and completely immersed in a water displacement tank [18,19]. For the determination of elastic modulus, the cuboidal specimen was mounted within an electromechanical load frame (Model 42) and compressed slowly by a flat-surface loading platen at a crosshead speed of 2.54 mm/min until 25% deformation in the loading direction was reached. The attached load cell had a resolution of 2.5 N. Strain was measured by the crosshead movement with a position resolution of 5×10^{-5} mm. The elastic modulus of the specimen was then extracted from the initial, linear portion of the stress–strain curve obtained during the loading

Table 1
Constituents of NIPAM-based hydrogel phantoms.

	NIPAM-42	NIPAM-52
Degassed water	150 ml	150 ml
AAc	0.19 ml	0.44 ml
NIPAM	9 g	9 g
MBAm	0.375 g	0.375 g
APS	0.195 g	0.195 g
TEMED	0.4 ml	0.4 ml